

Dissertation zur Erlangung des Doktorgrades
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**NEW PREPARATIONS AND REACTIONS OF SALT STABILIZED
ORGANOZINC REAGENTS FOR THE FUNCTIONALIZATION OF
AROMATICS, HETEROAROMATICS, AND ALLYLIC COMPOUNDS**

von

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aus

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ERKLÄRUNG

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EIDESSTATTLICHE VERSICHERUNG

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München,

.....

(Mario F. Ellwart)

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- 2) “Preparation of Tertiary Amines by the Reaction of Iminium Ions Derived from Unsymmetrical Amins with Zinc and Magnesium Organometallics”
V. Werner, M. Ellwart, A. J. Wagner, P. Knochel, *Org. Lett.* **2015**, *17*, 2026.
- 3) “Preparation of Solid, Substituted Allylic Zinc Reagents and Their Reactions with Electrophiles”
M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662; *Angew. Chem.* **2015**, *127*, 10808.
- 4) “Transition Metal Free Allyl-Allyl Cross-Couplings”
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- 7) “Preparation of Solid Organozinc Pivalates and their Reaction in Cross-Couplings”
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B) Reviews

“Polyfunctional Zinc and Magnesium Organometallics for Organic Synthesis: Some Perspectives”

A. D. Benischke, M. Ellwart, M. R. Becker, P. Knochel, *Synthesis* **2016**, 48, 1101.

C) Patents

“Organozinc Reagents and Processes for Preparing and Using the Same”

M. Ellwart, P. Knochel, EP 3070083, WO 2016146689, *an international patent application has been filed.*

“If you don't become the ocean, you'll be seasick every day.”

Leonard Cohen (1934–2016)

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Abbreviations

Ac	acetyl	<i>i</i> Pr	<i>iso</i> -propyl
acac	acetylacetone	IR	infrared
Ar	undefined aryl substituent	LDA	lithium diisopropylamide
ATR	attenuated total reflection	M	mol/L
aq. sat.	aqueous, saturated	M	Metal
Bn	benzyl	Me	methyl
Boc	<i>tert</i> -butoxycarbonyl	min	minute(s)
Bu	butyl	M.p.	melting point
dba	dibenzylideneacetone	MOM	methoxymethyl acetal
DCM	dichloromethane	MS	mass spectrometry
calcd.	calculated	n.d.	not determined
CCDC	Cambridge Crystallographic Data Center	NMR	nuclear magnetic resonance
conc.	concentrated	OPiv	pivalate (OCO <i>t</i> Bu)
d	day(s)	PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
d	doublet (NMR)	Ph	phenyl
DMAP	4-(dimethylamino)pyridine	ppm	parts per million
DMF	dimethylformamide	q	quartet (NMR)
DMPU	<i>N,N'</i> -dimethylpropyleneurea	R	undefined organic substituent
DMSO	dimethyl sulfoxide	s	singlet (NMR)
d.r.	diastereomeric ratio	SEM	2-(trimethylsilyl)ethoxymethyl
E	electrophile	SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
EI	electron ionization (MS)	TBAF	tetra- <i>n</i> -butylammonium fluoride
Et	ethyl	<i>t</i> Bu	<i>tert</i> -butyl
equiv./eq.	equivalents	TBS	<i>tert</i> -butyldimethylsilyl
ESI	electrospray ionization (MS)	TMDAM	tetramethyl diaminomethane
FDA	U.S. Food and Drug Administration	TFAA	trifluoroacetic anhydride
FG	functional group	tfp	tri(2-furyl)phosphine
GC	gas chromatography	THF	tetrahydrofuran
h	hour(s)	TIPS	triisopropylsilyl
HetAr	undefined heteroaryl substituent	TMP	2,2,6,6-tetramethylpiperidyl
Hex	hexyl	TMS	trimethylsilyl
HRMS	high resolution mass spectroscopy	TP	typical procedure
		UV	ultraviolet

A. INTRODUCTION

1 Overview

The FDA's Center for Drug Evaluation and Research approved 45 new drugs in 2015 which marks a 19-year high, exceeding even the previous recent record of 41 drugs in 2014.¹ This number shows that the constantly increasing search for novel biologically active molecules for the pharmaceutical industry is still one of the major areas of chemical research. The majority of the new therapeutic drugs (33) are still categorized in the broad class of small organic molecules with a low molecular weight ($< 900 \text{ g mol}^{-1}$). Sonidegib (Odomzo®, Novartis, anticancer, **1**), Palbociclib (Ibrance®, Pfizer, anticancer, **2**), Flibanserin (Addyi®, Sprout Pharmaceuticals, hypoactive sexual desire disorder treatment, **3**), and Panobinostat (Farydak®, Novartis, anticancer, **4**) are four examples of such molecules (Figure 1). New drug candidates are nowadays identified as such with the use of chemical libraries of synthetic small molecules or natural products in a process known as classical pharmacology in which the synthetic organic chemist plays a fundamental role.²

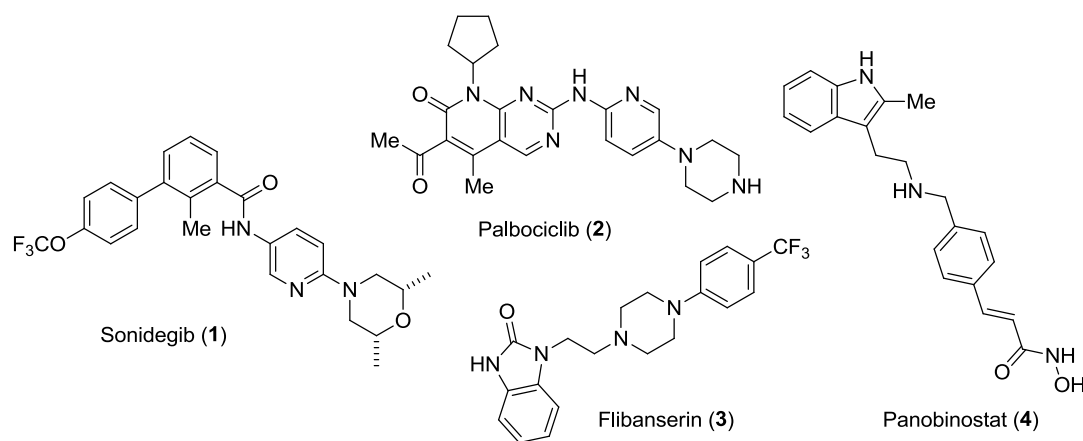


Figure 1: Selected small molecules approved as therapeutic drugs in the U.S. by the FDA in 2015.

In order to meet the high needs in quantity and complexity of the target molecules novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalized moieties are required. Organometallic reagents provide a general entry into complex molecules and many applications in total synthesis have been described.³ To achieve an efficient and selective formation of a new C–C bond with an organometallic compound the origin of the reagent is crucial. Organolithium compounds display an exceptional reactivity toward a variety of electrophiles due to the high ionic nature of the carbon–lithium bond (Figure 2). However, due to the high reactivity of organolithium reagents low reaction temperatures are often necessary and only few functional groups are tolerated in the course of the reaction. By using magnesium and aluminum compounds some of these drawbacks can be overcome as the carbon–metal bond is less polarized and thus displays a somewhat lower reactivity.

¹ A. Mullard, *Nat. Rev. Drug Discovery* **2016**, *15*, 73.

² J. A. Lee, M. T. Uhlik, C. M. Moxham, D. Tomandl, D. J. Sall, *J. Med. Chem.* **2012**, *55*, 4527.

³ K. C. Nicolaou, J. S. Chen, in *Classics in Total Synthesis III*, Wiley-VCH Verlag GmbH, **2011**.

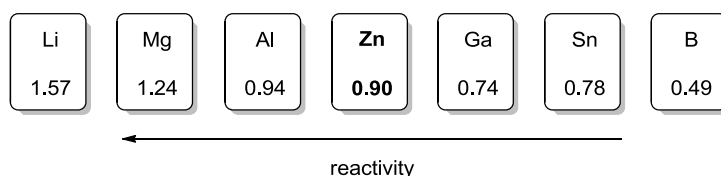


Figure 2: Electronegativity difference of selected metals relative to carbon (Pauling electronegativity scale).⁴

On the other hand, gallium, tin, and boron which form covalent bonds with carbon can tolerate a range of functional groups, but also show a very limited reactivity toward many electrophiles. The middle of the spectrum is occupied by zinc, which enables both, broad functional group tolerance as well as sufficient reactivity with a variety of reaction partners.

2 Organozinc Compounds

2.1 Overview

The chemistry of organozinc compounds dates back into a long history of scientific breakthroughs. Diethyl- and dimethylzinc, the first organozinc compounds were already prepared in 1849 by Frankland.⁵ Since then, organozinc compounds have found numerous applications in organic synthesis. The Reformatsky reaction⁶ or the Simmons-Smith cyclopropanation⁷ are only two examples. In addition, organozinc compounds have proved to easily undergo transmetalation reactions with various transition metals such as copper due to the presence of empty p-orbitals of appropriate energy which facilitates 4-membered transition states leading to mixed zinc-copper species. The resulting reagents, although being thermodynamically more stable (more covalent carbon–copper bond) are more reactive due to the presence of nucleophilic, nonbonding d-electrons that interact in an oxidative process with the electrophile and mediate the formation of the new carbon-carbon bond.⁸ The facile transmetalation to palladium in the Negishi cross-coupling reaction made organozinc compounds again a powerful and indispensable tool in organic synthesis resulting in rewarding Ei-ichi Negishi among Richard F. Heck and Akira Suzuki with the Nobel Prize in Chemistry in 2010 for their work on this new type of C–C bond formation.⁹ Organozinc reagents could be regarded as the most advantageous reagents in cross-coupling reactions due to their high functional group tolerance, whilst a good reactivity and non-toxic

⁴ A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, 39, 4414.

⁵ E. Frankland, *Liebigs Ann. Chem.* **1849**, 71, 171.

⁶ a) S. Reformatsky, *Chem. Ber.* **1887**, 20, 1210; **1895**, 28, 2842; b) R. Ocampo, *Tetrahedron* **2004**, 60, 9325.

⁷ a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, 80, 5323; b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, 81, 5323; c) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, 103, 977.

⁸ P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel, in *Handbook of Functionalized Organometallics*, Wiley-VCH Verlag GmbH, **2008**, pp. 251.

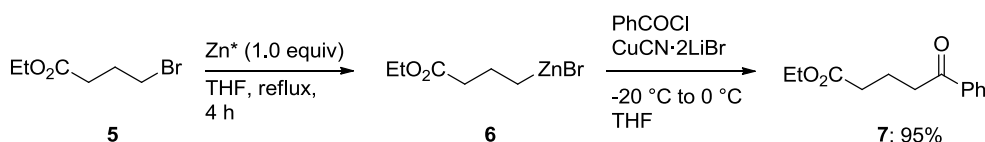
⁹ X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, 49, 9047.

byproducts.¹⁰ A major drawback is their lability when exposed to air which is believed to be mainly attributed to the hydrolysis *via* air moisture.

2.2 Preparation of Organozinc Compounds

2.2.1 Oxidative Insertion

Similarly to the preparation of organomagnesium compounds, the most common method for the direct synthesis of organozinc reagents is the insertion of zinc powder into organic halides. However, in many cases expensive organic iodides have to be used and elevated reaction temperatures are necessary. To avoid these drawbacks, Rieke et al. used highly active zinc (Zn^*), prepared by reduction of ZnCl_2 with lithium naphthalide to obtain functionalized organozinc reagents from less reactive arylbromides (Scheme 1).¹¹ Thus, starting from ethyl 4-bromobutyrate (**5**) the organozinc bromide (**6**) was obtained using the Rieke zinc, which led after addition of benzoyl chloride in the presence of $\text{CuCN} \cdot 2\text{LiBr}$ to the desired ethyl 5-oxo-5-phenylpentanoate (**7**) in 95% yield over two steps.



Scheme 1: Zinc insertion using Rieke zinc and subsequent acylation.^{11b}

Knochel and co-workers were able to show that also the use of commercial available zinc powder is suitable for the insertion into highly functionalized halides at mild conditions in the presence of LiCl (Scheme 2).¹² This allowed for the preparation of aromatic, heteroaromatic, and benzylic zinc reagents in the presence of a variety of functional groups like esters, nitriles, and aldehydes. The role of LiCl has been investigated by means of experimental, computational, and analytical studies.¹³ An additional positive effect of LiCl is the increased solubility of the organometallic reagent in THF solution and thus in the insertion reaction a free metal surface is regenerated which allows a further reaction with the starting halide.^{12a,14} Thus, the heteroaromatic bromide **8** could be transformed into the corresponding

¹⁰ a) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; d) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichimica Acta* **2009**, *42*, 71.

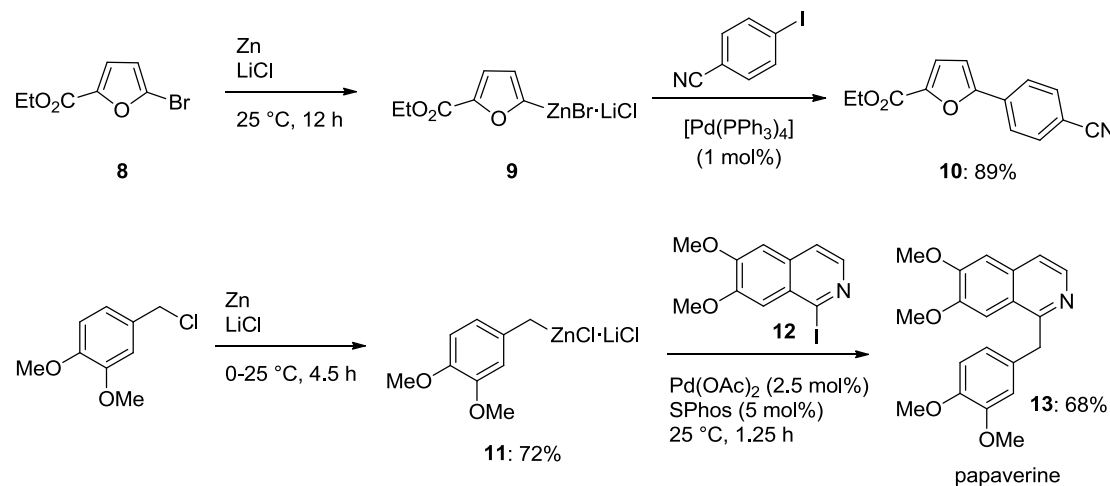
¹¹ a) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4322. b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

¹² a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; *Angew. Chem.* **2006**, *118*, 6186; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.

¹³ a) C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780. a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771; b) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

¹⁴ a) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159; b) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156.

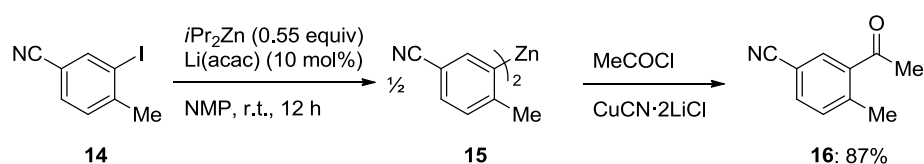
organozinc compound **9** under mild conditions and subsequently undergo a palladium catalyzed cross-coupling to the arylated product **10**. Furthermore the preparation and cross-coupling of the benzylic zinc reagent **11** with 1-iodo-6,7-dimethoxyisoquinoline (**12**) to furnish the opium alkaloid antispasmodic drug papaverine (**13**) was described.^{12a,b}



Scheme 2: Preparation of functionalized organozinc reagents using zinc dust in the presence of LiCl.^{12a,b}

2.2.2 Iodine-Zinc Exchange

Starting from organic iodides, the organozinc compound can alternatively be prepared by an exchange reaction using another organozinc reagent. The driving force in this reaction is the formation of the more stable organometallic reagent.¹⁵ Thus, for example the reaction of 3-iodo-4-methylbenzonitrile (**14**) with $i\text{Pr}_2\text{Zn}$ in the presence of Li(acac) as promoter for an intermediate ate complex formation leads to the diaromatic zinc reagent **15** and can be transformed in a copper catalyzed acylation to 3-acetyl-4-methylbenzonitrile (**16**) in 87% yield (Scheme 3).^{16,17}



Scheme 3: Preparation of diorganozincs by an Li(acac)-mediated iodine-zinc exchange reaction.¹⁶

2.2.3 Metalation

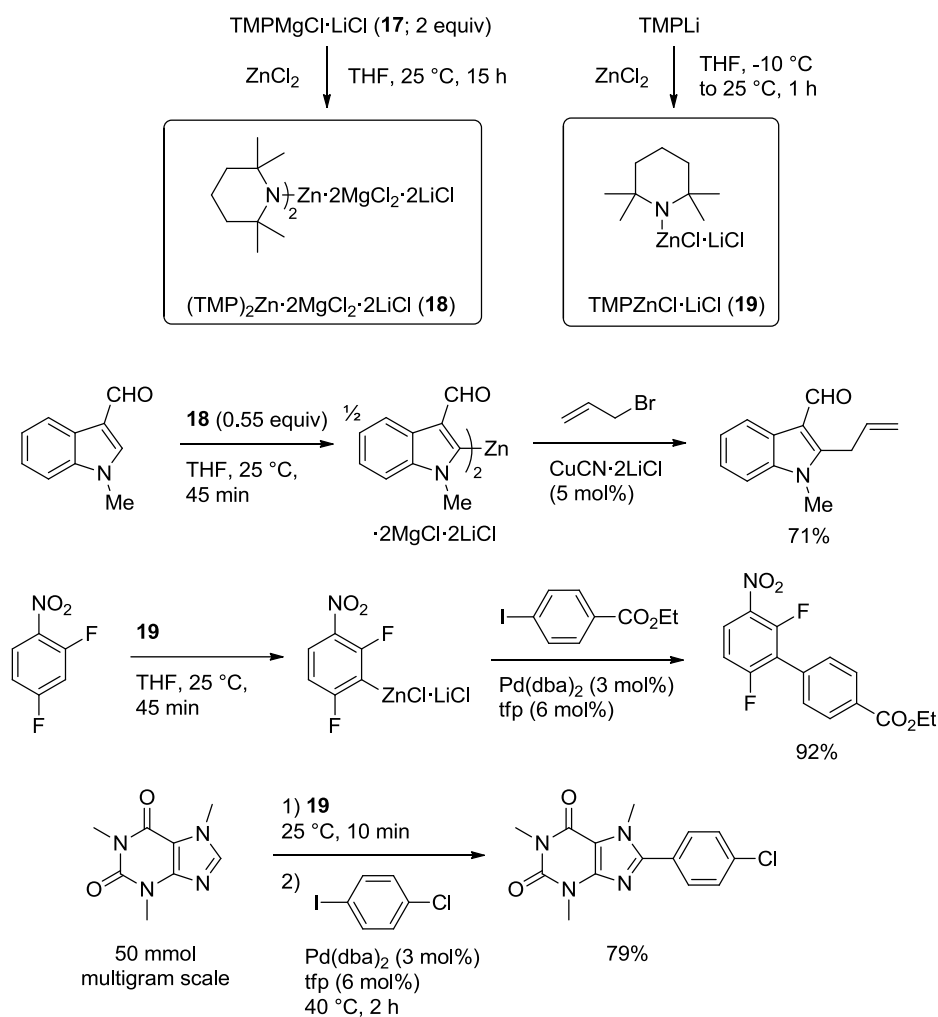
A different approach toward functionalized organometallics is the direct metalation using metal bases. Traditionally, strong bases such as alkyllithium reagents and lithium amides (R_2NLi ; e.g., LDA) have been extensively used for this purpose. However, they often suffer under undesired side reactions due to their high reactivity, their strong nucleophilicity, and their low functional group tolerance. Another

¹⁵ D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

¹⁶ F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

¹⁷ G. Dunet, P. Knochel, *Synlett*, **2007**, 1383.

serious drawback is the low stability of organolithium reagents in THF at ambient temperature. Thus, low temperatures (-78 to -100 °C) are often necessary for these reactions. A major improvement in this respect was the development of the highly active mixed Mg/Li-bases of type $R_2NMgCl \cdot LiCl$ by Knochel et al.¹⁸ $TMPMgCl \cdot LiCl$ (**17**) has been extensively used in the metalation of a variety of substrates.¹⁹ However, the resulting magnesium reagents also suffer from high reactivity and therefore have a limited functional group tolerance. As a logical consequence, Knochel et al. developed the highly chemoselective TMP-derived bases $(TMP)_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**18**) and $TMPZnCl \cdot LiCl$ (**19**) for the metalation of sensitive aromatics and heterocycles under mild conditions (Scheme 4).^{20,21}



Scheme 4: Knochel bases **18** and **19** for the regioselective metalation and functionalization of aromatic and heteroaromatic scaffolds.^{20a,21}

¹⁸ a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) T. Kunz, P. Knochel, *Angew. Chem.* **2012**, *124*, 1994; *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

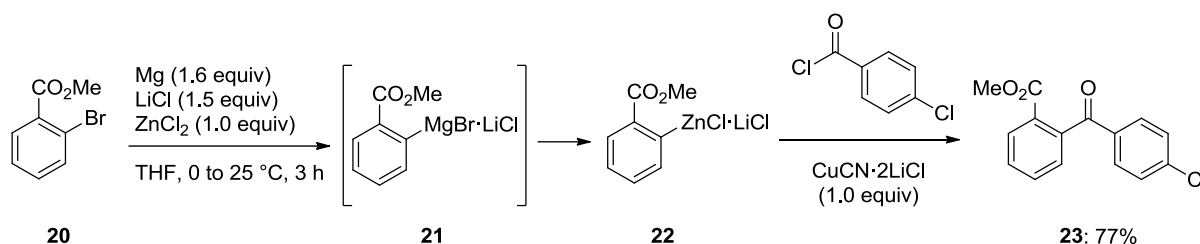
¹⁹ For an overview see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794. S. M. Manolikakes, N. M. Barl, C. Sämann, P. Knochel, *Z. Naturforsch., B: Chem. Sci.* **2014**, *68*, 411; T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253.

²⁰ S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 339;

²¹ M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299.

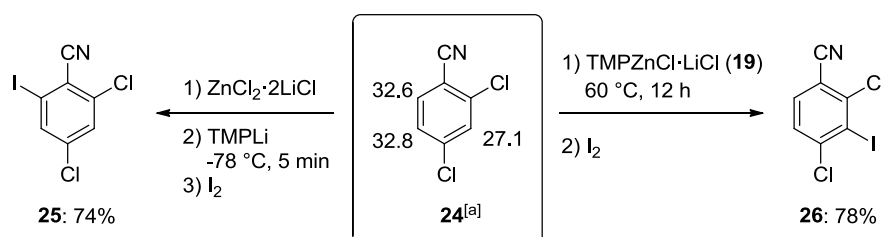
2.2.4 Transmetalation

The treatment of organomagnesium or organolithium compounds with ZnCl_2 solution in THF leads to a transmetalation to the corresponding organozinc compounds. The driving force is the formation of the more covalent and hence more stable C–Zn bond. For example the magnesium insertion into methyl 2-bromobenzoate (**20**) in the presence of ZnCl_2 leads to an intermediate formation of the magnesium compound **21** but is trapped by the zinc salt before intramolecular side reactions can occur leading to the stable zinc compound **22**.²² Acylation in the presence of $\text{CuCN}\cdot 2\text{LiCl}$ furnishes the desired ketone **23** in 77% overall yield.



Scheme 5: Magnesium insertion in the presence of ZnCl_2 .²²

The lithiation of arenes and heteroarenes is an important tool for the functionalization of complex aromatic scaffolds. However, the resulting lithium derivatives suffer from an exceptionally high reactivity and thus are limited in terms of functional group tolerance. Knochel et al. reported a procedure which allows for the concomitant use of TMPLi with various metal salts such as MgCl_2 , ZnCl_2 or CuCN . Thus, the metalation of 2,4-dichlorobenzonitrile (**24**) using TMPLi in the presence of $\text{ZnCl}_2\cdot 2\text{LiCl}$ and subsequent addition of iodine leads to the kinetic iodinated product (**25**) whereas the use of $\text{TMPZnCl}\cdot \text{LiCl}$ (**19**) leads to a metalation in the most acidic position 3 furnishing **26**.²³ Furthermore, it was shown that the reaction of TMPLi with **24** is more than six times faster than the reaction of TMPLi with $\text{ZnCl}_2\cdot 2\text{LiCl}$ which allows for the high regioselectivity in this transformation.



Scheme 6: Regioselectivity switch in the metalation of **24** using TMPLi in the presence of $\text{ZnCl}_2\cdot \text{LiCl}$ or $\text{TMPZnCl}\cdot \text{LiCl}$ (**19**). [a] Calculated pK_a values for H3, H5, and H6.²³

²² F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192

²³ A. Frischmuth, M. Fernández, N. M. Barl, F. Achraimer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928; *Angew. Chem.* **2014**, *126*, 8062.

3 Solid, Salt Stabilized Organozinc Reagents

3.1 Overview

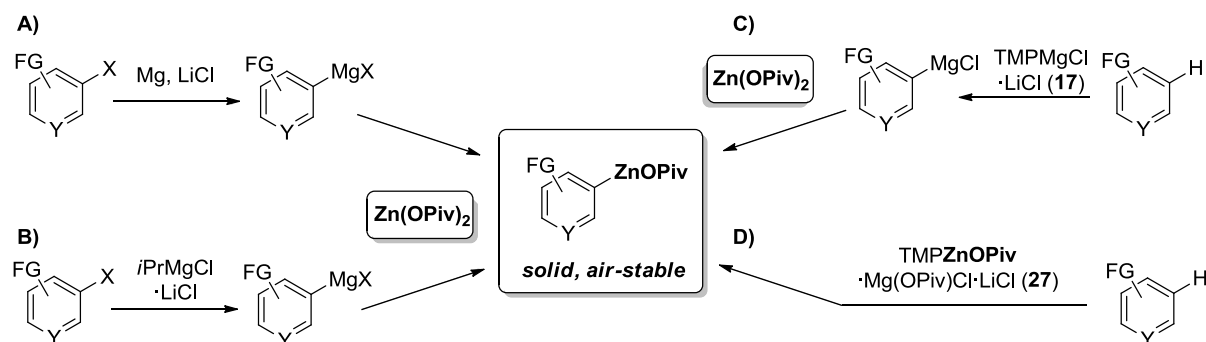
As described in Chapter 2, organozinc reagents play a major role in organometallic chemistry due to their high compatibility with a broad variety of functional groups. Moreover, they are valuable reagents for transition metal mediated C–C bond formation reactions, such as Negishi cross-coupling,²⁴ allylation,²⁵ or acylation²⁶ reactions. However, their limited stability towards air and moisture represents a serious drawback for their practical use in the laboratory and for industrial applications. To overcome this problem, we recently developed a method for the preparation of aryl and heteroaryl zinc pivalates, which are easy-to-handle solids with exceptional stability when exposed to air.²⁷ These zinc reagents can be prepared by magnesium insertion or halogen–magnesium exchange followed by transmetalation with $\text{Zn}(\text{OPiv})_2 \cdot 2\text{LiCl}$ (OPiv = pivalate) to give the corresponding aryl, heteroaryl, and benzylic zinc reagents described with the proposed formula $\text{RZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{X} \cdot 2\text{LiCl}$ (X = Cl, Br, I) (Scheme 7, A and B).^{27a} A halogen–lithium exchange followed by transmetalation with $\text{Zn}(\text{OPiv})_2$ proved to be a feasible way to prepare 2-pyridylzinc reagents.^{27d} Another possible route is directed metalation using the sterically hindered base $\text{TMPMgCl} \cdot \text{LiCl}$ (**17**)^{18,19} and subsequent addition of $\text{Zn}(\text{OPiv})_2$, giving organozinc reagents described as $\text{RZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{Cl} \cdot \text{LiCl}$ (Scheme 7, C). The air-stability of such zinc organometallics was substantially superior to organozinc pivalates prepared by magnesium insertion (or exchange).^{27b} In the presence of sensitive functionalities such as an aldehyde or a nitro group, the milder zinc amide base $\text{TMPZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{Cl} \cdot \text{LiCl}$ ^{27c} (**27**) may be used for highly selective metalation reactions to give the desired organozinc reagents, which undergo a range of reactions with various electrophiles (Scheme 7, D).

²⁴ a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118; d) E. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), 2nd ed., Wiley-VCH, Weinheim, **2004**; e) A. A. Zemtsov, N. S. Kondratyev, V. V. Levin, M. I. Struchkova, A. D. Dilman *J. Org. Chem.* **2014**, *79*, 818.

²⁵ a) F. Dübner, P. Knochel, *Angew. Chem.* **1999**, *111*, 391; *Angew. Chem. Int. Ed.* **1999**, *38*, 379; b) F. Dübner, P. Knochel, *Tetrahedron*, **2000**, *41*, 9233; c) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169; d) C. A. Falcicola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; e) K. Geurts, S. P. Fletcher, A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *Pure Appl. Chem.* **2008**, *5*, 1025; f) E. Erdik, M. Koçoğlu, *J. Organomet. Chem.* **2009**, *694*, 1890.

²⁶ a) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1982**, *106*, 3368; b) P. Knochel, M. Yeh, S. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; c) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990**, *112*, 6146.

²⁷ a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem.* **2011**, *123*, 9372; *Angew. Chem. Int. Ed.* **2011**, *50*, 9205; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem.* **2012**, *124*, 9563; *Angew. Chem. Int. Ed.* **2012**, *51*, 9428; c) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302; d) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754; e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.



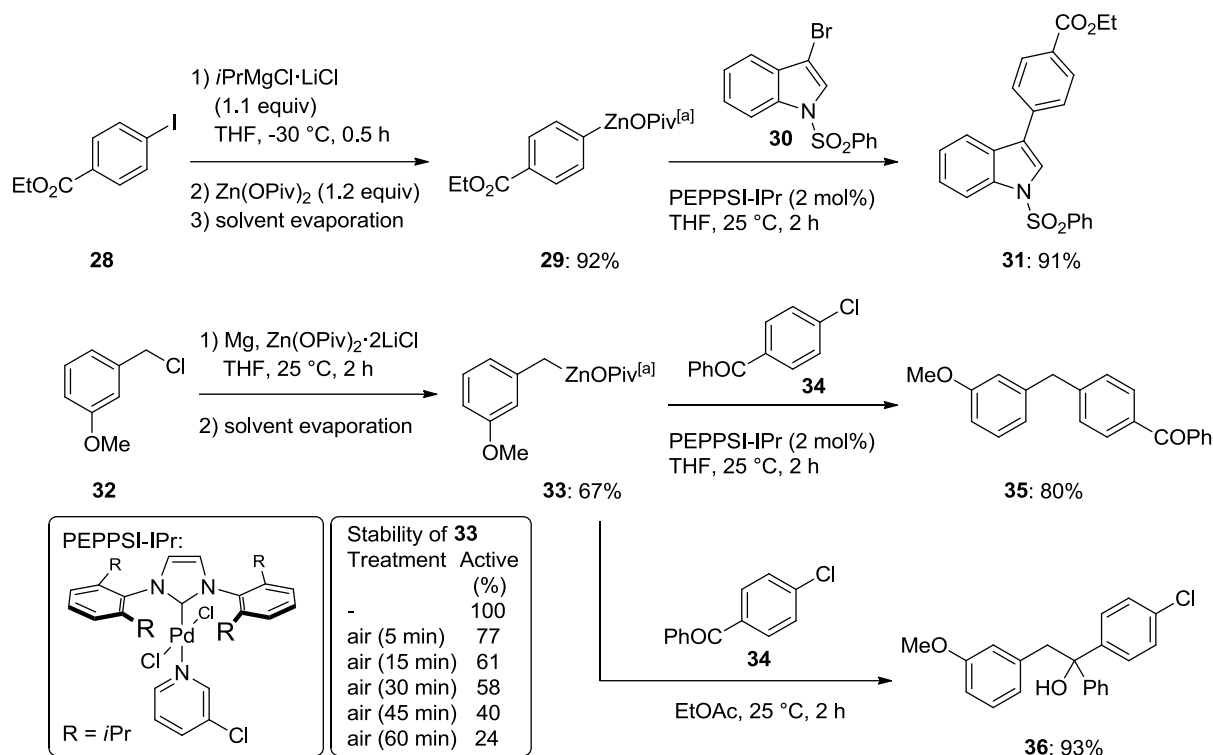
Scheme 7: Different protocols for the preparation of (hetero-)aromatic organozinc pivalates.^{27a-c,e}

The structure of the resulting zinc reagents is complex due to the presence of various metal salts in the final reagents.^{27a} Structural studies in solution and on the crystal performed by Mulvey and Hevia indicate that the addition of solid zinc pivalate leads to a complete transmetalation to the corresponding organozinc halide and Mg(OPiv)_2 , which then acts as an air and moisture scavenger and is hence responsible for the exceptional air-stability of the reagents.²⁸ Therefore, a more accurate way to describe these trimetallic clusters would be the general formula: “ $\text{RZnX} \cdot \text{Mg(OPiv)}_2 \cdot n\text{LiCl}$ ” ($\text{X} = \text{Br, I, Cl}$; $n = 1\text{--}2$). For clarity, the abbreviation RZnOPiv was used in this thesis.

3.2 Preparation of Organozinc Pivalates from (Hetero-)Aryl Halides

As mentioned in Chapter 3.1 starting from (hetero-)aromatic or benzylic halides the magnesium insertion reaction in the presence of LiCl at ambient temperature followed by addition of solid Zn(OPiv)_2 led to the corresponding organozinc pivalates. Exchange reactions were performed by using $i\text{PrMgCl} \cdot \text{LiCl}$ (1.1 equiv) at low temperature and subsequent transmetalation with Zn(OPiv)_2 gave the desired organozinc pivalates. In both cases, the solid organozinc pivalates were obtained after solvent evaporation in high vacuum (0.1 mmHg, 3–6 h). Thus, the addition of $i\text{PrMgCl} \cdot \text{LiCl}$ to ethyl 4-iodobenzoate (**28**) and subsequent transmetalation with solid Zn(OPiv)_2 led to the solid, air-stable zinc reagent **29** which underwent a PEPPSI-IPr catalyzed cross-coupling reaction with the indole derivative **30** producing the desired product **31** in 91% yield (Scheme 8). Starting from 1-(chloromethyl)-3-methoxybenzene (**32**) the insertion of magnesium in the presence of the THF-soluble salt $\text{Zn(OPiv)}_2 \cdot 2\text{LiCl}$ leads to the benzylic zinc reagent **33** which after addition of 2 mol% PEPPSI-IPr and aryl chloride **34** produces the cross-coupling product **35** in 80% yield. However, when no Pd-catalyst is added to a solution of the reagent in EtOAc the addition of **35** leads to the tertiary alcohol **36** in 93% yield. The solid reagent **33** shows an increased stability when exposed to air since 24% of active species is still retained after 60 min (Scheme 8).

²⁸ A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, 53, 2706; *Angew. Chem.* **2014**, 126, 2744.



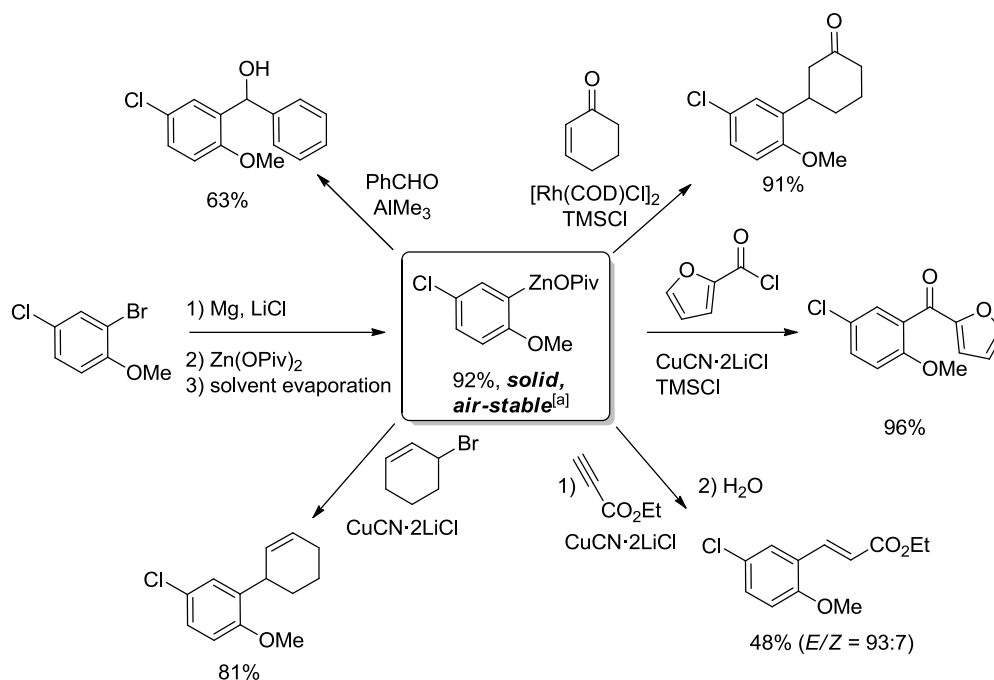
Scheme 8: Preparation of solid, salt stabilized organozinc reagents and their application in Negishi cross-coupling reactions and additions to carbonyls. [a] Complexed Mg(OPiv)X and LiCl are omitted for clarity.

Furthermore we found recently, that these solid zinc reagents do not only show an excellent reactivity in Negishi cross-coupling reactions and have investigated the reactivity of organozinc pivalates in 1,4-additions,²⁹ carbocuprations³⁰ as well as allylations, acylation reactions and their addition to aldehydes (Scheme 9).^{27e,31}

²⁹ Rh-catalysis: a) M. Sakai, H. Hayashi, N. Miyaoura, *Organometallics* **1997**, *16*, 4229; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; c) T. Hayashi, *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 2595; d) J. Le Nôtre, D. van Mele, C. G. Frost, *Adv. Synth. Catal.* **2007**, *349*, 432; e) J. C. Allen, G. Kociok-Köhn, C. G. Frost, *Org. Biomol. Chem.* **2012**, *10*, 32; Cu-catalysis: f) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *34*, 4029; g) V. Wendisch, N. Sewald, *Tetrahedron Asymmetry*, **1997**, *8*, 1253; h) M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999; i) A. Wilsily, E. Fillion, *Org. Lett.* **2008**, *10*, 2801; j) A. Wilsily, T. Lou, E. Fillion, *Synthesis* **2009**, *12*, 2066; k) A. Quintarda, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 1856; l) M. Tissot, A. Pérez Hernández, D. Müller, M. Mauduit, A. Alexakis, *Org. Lett.* **2011**, *13*, 1524.

³⁰ a) H. Chechik-Lankin, I. Marek, *Synthesis* **2005**, *19*, 3311; b) A. Abramovitch, I. Marek, *Eur. J. Org. Chem.* **2008**, 4924; c) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128; d) B. Dutta, N. Gilboa, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 5588; e) C. Dunst, A. Metzger, E. A. Zaburdaeva, P. Knochel, *Synthesis* **2011**, 3453; f) A. Frischmuth, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10084; g) Y. Minko, M. Pasco, H. Chechik, I. Marek, *Beilstein J. Org. Chem.* **2013**, *9*, 526; h) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah, G. Evano, *Org. Lett.* **2013**, *15*, 3122; For reviews on carbocupration reactions see also: i) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841; j) N. Krause in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**; k) N. Chinkov, D. Tene, I. Marek in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), 2nd ed. Wiley-VCH, Weinheim, **2004**; l) A. Basheer, I. Marek, *Beilstein J. Org. Chem.* **2010**, *6*, 77.

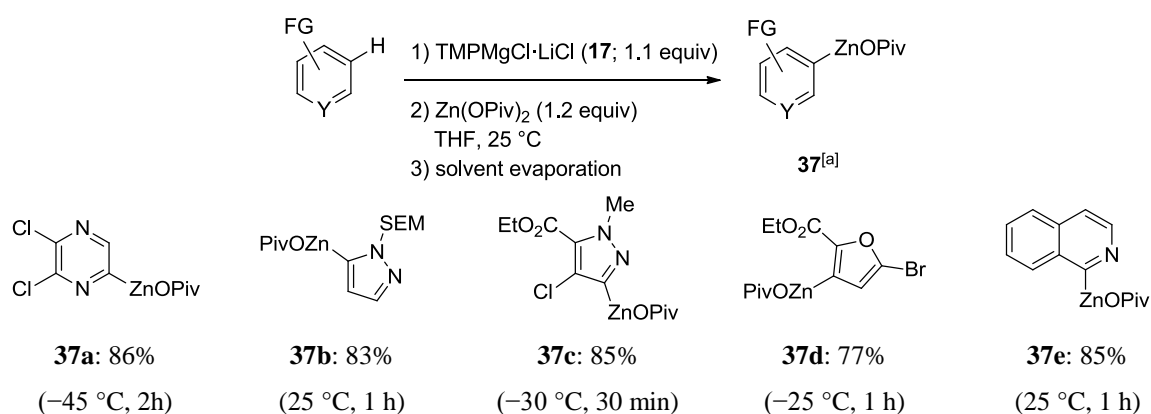
³¹ M. Ellwart, Master's Thesis, Ludwig-Maximilians-Universität München, **2013**.



Scheme 9: Selected examples for the extended applications of arylzinc pivalates. [a] Complexed Mg(OPiv)Br and LiCl are omitted for clarity.^{27e,31}

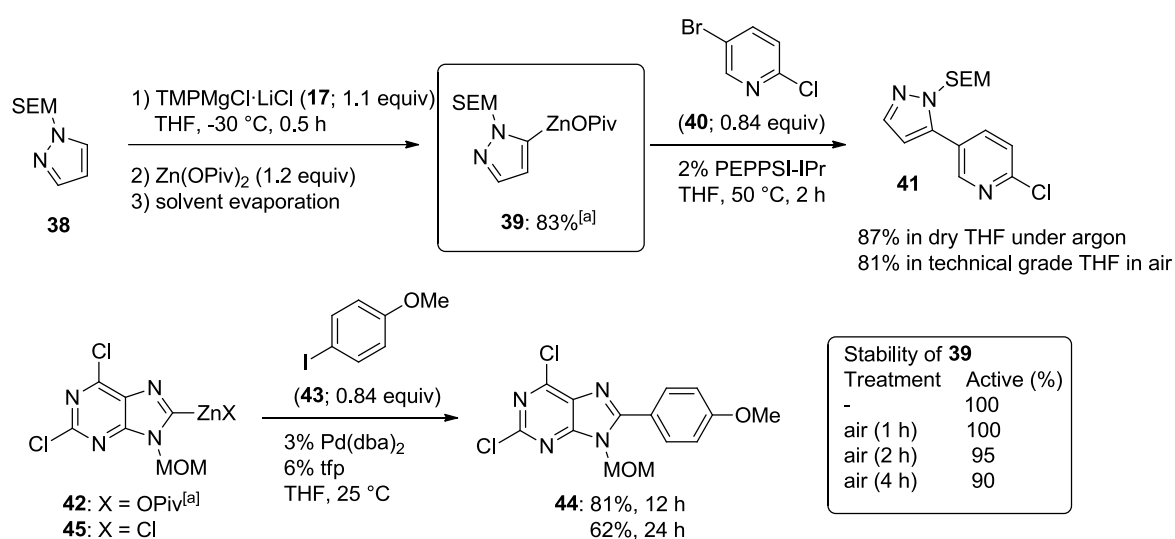
3.3 Preparation of Organozinc Pivalates by Metalation

Although aryl and heteroaryl halides used for the preparation of solid organozinc pivalates are readily available, it was envisioned that these organometallics could be prepared by directed metalation, which would allow to expand the scope of our preparations to include various arenes and heteroarenes as convenient starting materials. The sterically hindered base TMPMgCl·LiCl (**17**) was used to deprotonate various carbo- and heterocycles and the resulting magnesium reagents were transmetalated by using Zn(OPiv)₂ (Scheme 10).^{27b} This procedure gives access to a range of new solid zinc reagents of type **37** that show very high stability when exposed to air. As a general trend, the concentration of the new zinc reagents is almost entirely (>94%) preserved after 2 h of air exposure, while this percentage remains greater than 85% even after 4 h in air.



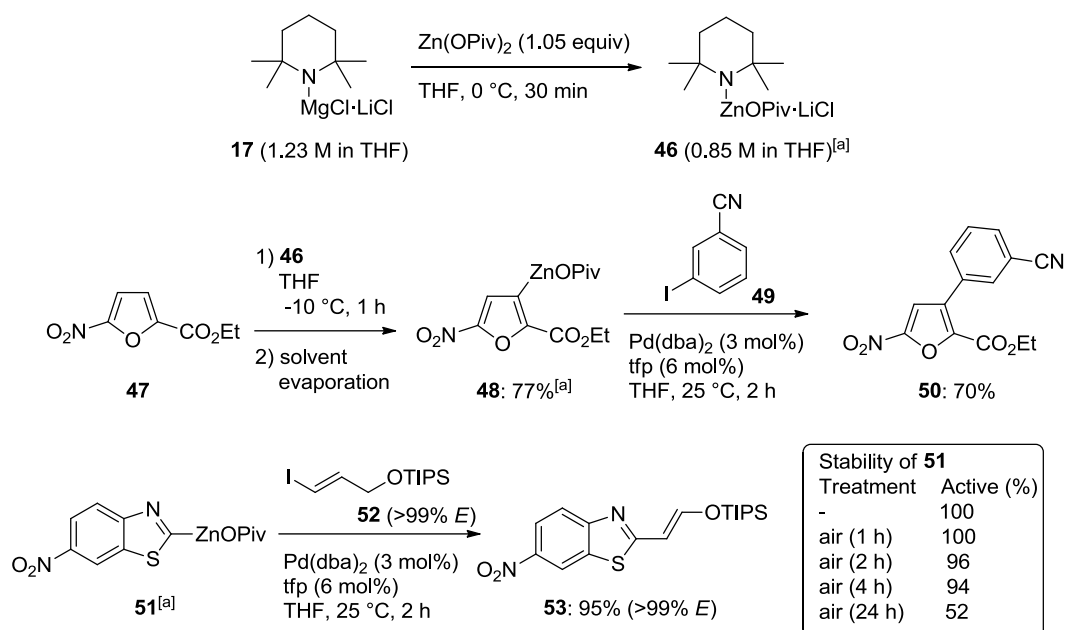
Scheme 10: Selected examples for the metalation of heterocycles using TMPMgCl·LiCl (**17**) followed by a transmetalation with Zn(OPiv)₂. [a] Complexed Mg(OPiv)X and LiCl are omitted for clarity.

In addition, these zinc reagents are stable for, at least, several months under argon or nitrogen in a closed vial. After redissolution of the solid zinc compound in dry THF (0.5 M), cross-coupling reactions as well as allylation or acylation reactions can be performed. Thus, pyrazole derivative **38** was readily metalated by using **17** (1.1 equiv., $-30\text{ }^{\circ}\text{C}$, 0.5 h) and led, after transmetalation with $\text{Zn}(\text{OPiv})_2$ (1.2 equiv), to the formation of zinc reagent **39** in 83% yield (Scheme 11). Addition of 2% PEPPSI-IPr and subsequently 5-bromo-2-chloropyridine (**40**, 0.84 equiv), led to the functionalized heterocyclic compound **41** in 87% yield after heating to $50\text{ }^{\circ}\text{C}$ for 2 h. Interestingly, the use of technical-grade THF in an open flask led to **41** with only a minor yield decrement (81%). Furthermore, 2,6-dichloropurinylyl zinc pivalate **42** was used in a Negishi cross-coupling with 4-iodoanisole (**43**) and furnished the functionalized purine derivative in 81% yield, while the corresponding organozinc chloride **45** required 24 h for completion and afforded the coupling product **44** in significantly lower yield.



Scheme 11: Preparation and stability of zinc pivalate **39** and Negishi cross-coupling in different qualities of THF. Comparison of the reactivity of 2,6-dichloropurinylyl zinc pivalate **42** and the corresponding zinc chloride **45** in Negishi cross-coupling with 4-iodoanisole **43**. [a] complexed $\text{Mg}(\text{OPiv})\text{Cl}$ and LiCl are omitted for clarity.

However, none of the methods above can be applied efficiently when sensitive functionalities are present. To overcome this limitation, Knochel *et al.* described the milder zinc amide base, $\text{TMPZnOPiv}\cdot\text{Mg}(\text{OPiv})\text{Cl}\cdot\text{LiCl}$ (**46**) which is compatible with functionalities like nitro groups, aldehydes, or sensitive heteroaromatic rings. In addition, it was shown that the new base **46** provided fast and efficient access, after removal of the solvent, to solid zinc pivalates, which exhibit significant tolerance towards hydrolysis or oxidation after air-exposure. $\text{TMPZnOPiv}\cdot\text{Mg}(\text{OPiv})\text{Cl}\cdot\text{LiCl}$ (**46**) is prepared by addition of solid $\text{Zn}(\text{OPiv})_2$ (1.05 equiv., $0\text{ }^{\circ}\text{C}$) to a solution of $\text{TMPMgCl}\cdot\text{LiCl}$ (**17**, 1.23 M in THF) and subsequent dilution with dry THF until a clear solution is formed (final concentration: 0.85–0.99 M, (Scheme 12).

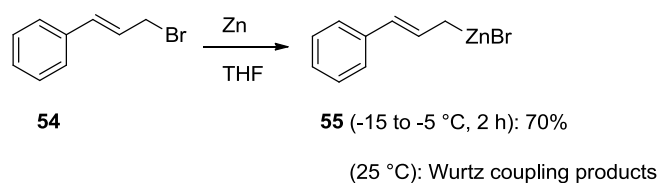


Scheme 12: Preparation and reactivity of $\text{TMPZnOPiv} \cdot \text{Mg(OPiv)Cl} \cdot \text{LiCl}$ (**46**) and selected examples for application and stability of the resulting organozinc pivalates. [a] complexed Mg(OPiv)Cl and LiCl are omitted for clarity.

Thus, using the base **46** ethyl 5-nitrofuran-2-carboxylate (**47**) can be readily metalated and after solvent evaporation the solid zinc reagent **48** is obtained in 77% yield. The reaction of the zinc reagent thus formed (**48**) in Negishi cross-coupling with the aryl iodide **49** led to the furan **50** in 70% yield. The solid and air-stable zinc reagent undergoes a palladium catalyzed coupling reaction with the *E*-alkenyl iodide **52** to furnish the coupling product **53** in 95% yield and with complete retention of the double-bond configuration (Scheme 12).

4 Allylzinc Compounds

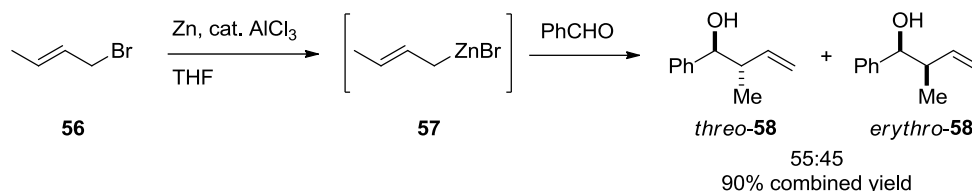
In 1962, Gaudemar reported the direct insertion of zinc into various allylic bromides furnishing allylzinc bromides in moderate to good yields.³² Cinnamyl bromide (**54**) was reacted with zinc in THF at -15 °C to -5 °C leading to cinnamylzinc bromide (**55**) in 70% yield (Scheme 13). The low temperature was necessary to avoid the formation of Wurtz coupling products.



Scheme 13: Preparation of cinnamylzinc bromide by Gaudemar.

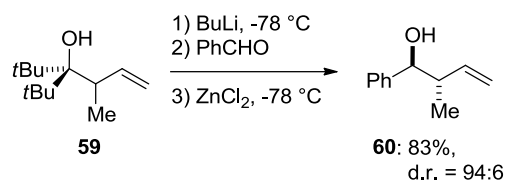
³² M. Gaudemar, *Bull. Soc. Chim. Fr.* **1962**, 974.

An alternative approach included an insertion of zinc induced by a catalytic amount of AlCl_3 (Scheme 14) leading to the intermediate organozinc compounds, which were then trapped by various carbonyl compounds. However, the diastereoselectivity was very poor as the reaction of crotyl bromide (**56**) and unactivated zinc using a catalytic amount of AlCl_3 to form crotylzinc bromide (**57**) and subsequent reaction with benzaldehyde led to both diastereomers with a combined yield of 90% and a d.r. of 55:45.³³



Scheme 14: Preparation of crotylzinc bromide (**57**) from crotyl bromide (**56**) and unactivated zinc induced by a catalytic amount of AlCl_3 and subsequent reaction with benzaldehyde.³³

The problem of Wurtz coupling and of poor diastereoselectivity were overcome by Knochel et al. who used masked allylic zinc reagents from a fragmentation reaction.³⁴ Thus, starting from the sterically hindered tertiary alcohol **59** addition of BuLi and ZnCl_2 led to the zinc alkoxide followed by a fragmentation to the corresponding allylic zinc reagent which in the presence of benzaldehyde reacts to the *anti*-diastereomer of benzylic alcohol **60** in 83% (d.r. = 94:6).

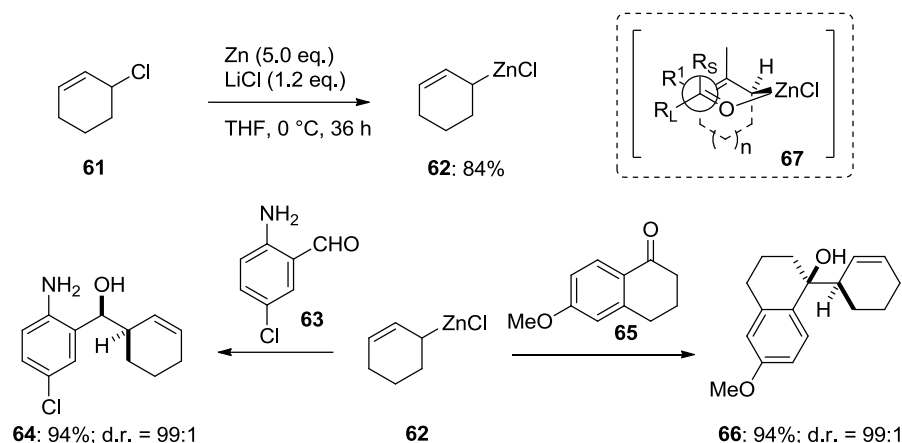


Scheme 15: Highly diastereoselective allylations using masked allylic zinc reagents.^{34b}

Later, it was found that the LiCl-mediated direct insertion of zinc powder to cyclic allylic chlorides leads to the corresponding allylic zinc reagents, forming only small amounts of Wurtz coupling products. These organometallics were found to add diastereoselectively to various carbonyl derivatives. Thus, the insertion of zinc dust into 3-chlorocyclohex-1-ene (**61**) in the presence of LiCl in THF leads after 36 h at 0 °C to the allylic zinc reagent **62** in 84% yield. **62** reacts with the aldehyde **63** even in the presence of a free $-\text{NH}_2$ group and delivers diastereoselectively the product **64** in 94% yield. Even ketone **65** can be used in the reaction with **62** to produce the homoallylic alcohol **66** in 94% yield (d.r. = 99:1). A cyclic 6-membered transition state **67** was proposed.

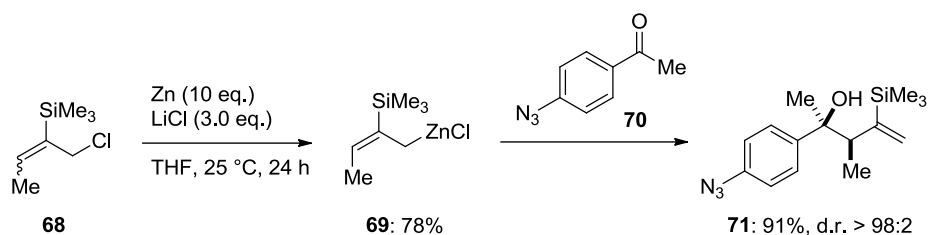
³³ H. Maeda, K. Shono, H. Ohmori, *Chem. Pharm. Bull.* **1994**, 42, 1808.

³⁴ a) P. Jones, N. Millot, P. Knochel, *Chem. Commun.* **1998**, 2405; b) P. Jones, P. Knochel, *Chem. Commun.* **1998**, 2407.



Scheme 16: Highly diastereoselective preparation of homoallylic alcohols bearing adjacent quaternary centers using substituted allylic zinc reagents.

In addition, this methodology was extended to silyl substituted crotylzinc reagents leading stereoselectively to *syn*-homoallylic alcohols.³⁵ For instance, the readily available trimethylsilyl substituted allyl chloride **68** underwent a smooth insertion reaction and provided organozinc species **69** in 78% yield as determined by iodometric titration (Scheme 17). Upon the addition of **69** to functionalized acetophenone **70** the allylation product **71** was obtained as a single diastereomer in 91% yield (d.r. > 98:2).

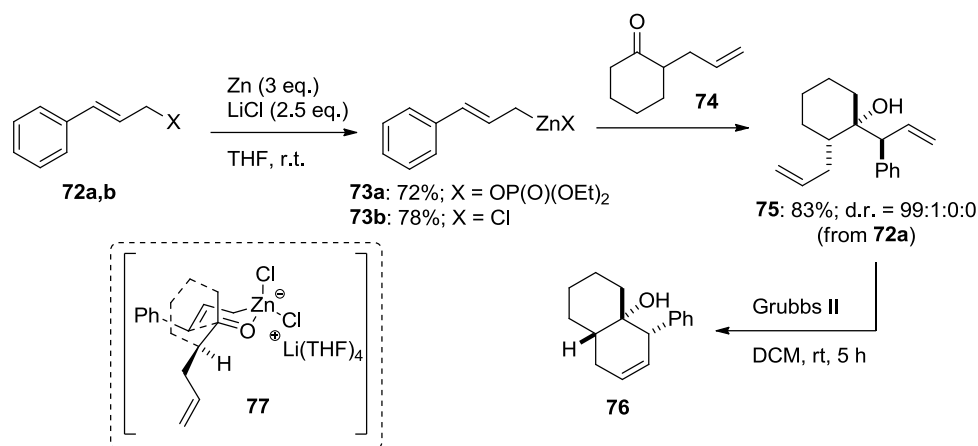


Scheme 17: Preparation of silyl substituted crotylzinc reagent **69** and subsequent reaction with acetophenone **70** with an azide functional group.³⁵

Furthermore, it was shown that the addition of cinnamylzinc reagents to α -chiral carbonyl compounds leads to homoallylic alcohols bearing three adjacent stereocenters with high diastereoselectivity.³⁶ The insertion of zinc into cinnamyl phosphate **72a** or chloride **72b** in the presence of LiCl led to the corresponding organozinc reagents **73a,b** in 72 and 78% yield respectively (Scheme 18). A subsequent reaction with 2-allylcyclohexanone (**74**) furnished the homoallylic alcohol **75** in 83% yield and high diastereoselectivity. Subsequent metathesis with Grubbs II catalyst (5 mol%) led to the bicyclic alcohol **76** in 93% yield. This diastereoselectivity was rationalized by considering a cyclic chair-like transition state **77**, where the allylic zinc reagent approaches from the sterically less crowded side (opposite side of the allyl group), as depicted in Scheme 18).

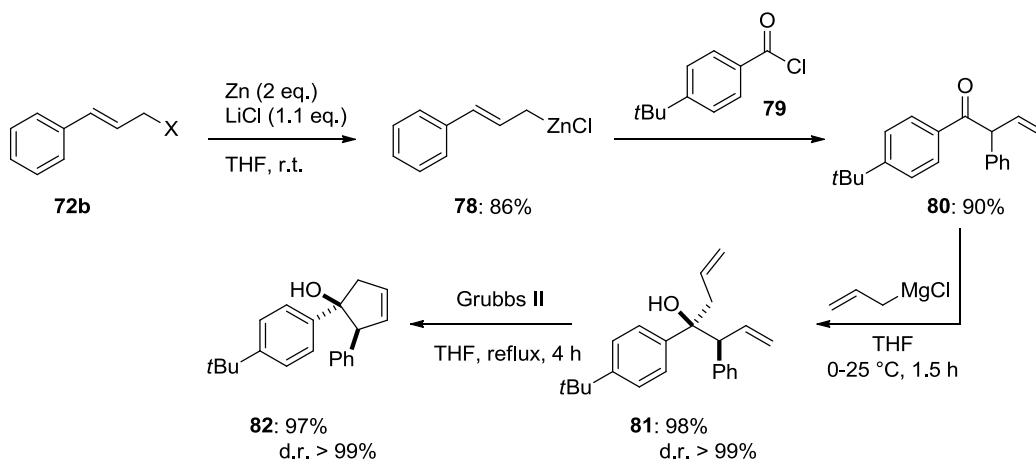
³⁵ M. D. Helm, P. Mayer, P. Knochel, *Chem. Commun.* **2008**, 1916.

³⁶ G. Dunet, P. Mayer, P. Knochel, *Org. Lett.* **2008**, 10, 117.



Scheme 18: Highly diastereoselective addition of cinnamylzinc derivatives to 2-allylcyclohexanone (**74**) and subsequent metathesis yielding bicyclic alcohol **76**. Proposed cyclic chair-like transition state **77**.³⁶

Recently, Knochel et al. reported a convenient synthesis of α -substituted β,γ -unsaturated ketones and esters by the addition of substituted allylic zinc reagents prepared by direct insertion. Thus, using cinnamyl chloride (**72b**) and only 2 equivalents of Zn and 1.1 equivalents of LiCl the corresponding organozinc chloride **78** was obtained in 86% yield and underwent a smooth acylation reaction with 4-(*tert*-butyl)benzoyl chloride (**79**) to yield the corresponding ketone **80** in 90% yield.³⁷ A diastereoselective addition of allylmagnesium chloride to **80** led to the diene precursor **81** which was used in a ring closing metathesis (RCM) reaction furnishing diastereoselectively the cyclopentene derivative **82** in 97% yield.

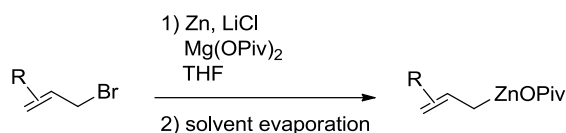


Scheme 19: Synthesis of α -substituted β,γ -unsaturated ketone **80** via the addition of allylic zinc reagent **78** to acid chloride **79**. Subsequent diastereoselective addition of allylmagnesium chloride and RCM.

³⁷ C. Sämann, P. Knochel, *Synthesis* **2013**, 1870.

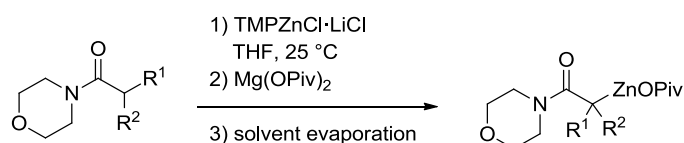
5 Objectives

Based on our results for the arylzinc pivalates and the recently reported versatile applications of allylzinc reagents we studied the preparation of the first solid allylic zinc compounds. Therefore, a novel protocol for the preparation of salt stabilized reagents starting from allylic bromides was investigated. As Mulvey and Hevia reported (Chapter 3.1), $\text{Mg}(\text{OPiv})_2$ is believed to play an important role in the increased stability of organozinc pivalates as an air- and moisture scavenger. Thus, it was envisioned that the addition of $\text{Mg}(\text{OPiv})_2$ during the zinc insertion might lead to stabilized allylic zinc pivalates (Scheme 20).



Scheme 20: Novel protocol for the preparation of allylic zinc pivalates.

Moreover, the concept of $\text{Mg}(\text{OPiv})_2$ as an additive for stabilizing organozinc compounds was extended to the preparation of Reformatsky reagents. Particularly, morpholine amides were studied as substrates for a selective metalation using TMPZnCl and $\text{Mg}(\text{OPiv})_2$ (Scheme 21).



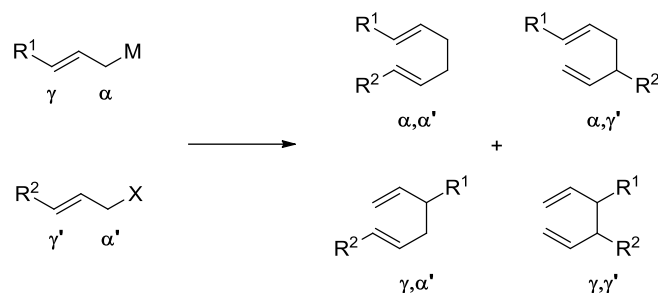
Scheme 21: Preparation of solid zinc amide enolates using TMPZnCl and $\text{Mg}(\text{OPiv})_2$.

Furthermore, due to the lack of a scalable protocol for the preparation of (hetero-)aryl pivalates a procedure was investigated to prepare these reagents in scales up to 70 mmol. A range of reagents should be prepared following this procedure in order to provide a set of reagents for high throughput screenings, e.g., in medicinal chemistry.



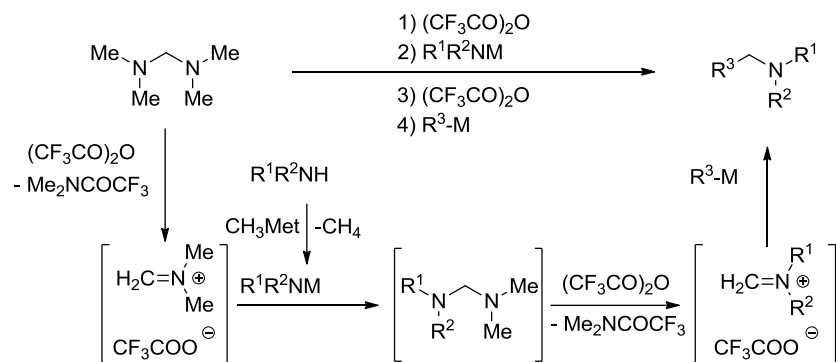
Scheme 22: Development of a scalable protocol for the preparation of (hetero-)arylzinc pivalates and subsequent scale-up cross-coupling.

Another subject dealt with the improvement of the selectivity of allyl-allyl cross-couplings toward the preparation of a single isomer out of four possible (Scheme 23). Allylic zinc compounds could be suitable reagents in this transformation due to their facile preparation and their tolerance of a variety of functional groups.



Scheme 23: Cross-coupling of allylic organometallics with allylic halides leading to four regioisomeric coupling products.

Finally, to develop a novel preparation of benzylamines or biologically relevant phenethylamines a new protocol was investigated starting from *N,N,N',N'*-tetramethylmethanediamine (Scheme 24).³⁸ After formation of Tieze's salt a mixed aminal should be produced which could then be reacted with trifluoroacetic anhydride. The resulting iminium ion could be suitable for a reaction with a range of organometallic species.



Scheme 24: One-pot reaction sequence for the preparation of benzylamines or phenethylamines.

³⁸ This project was developed in cooperation with V. Werner and A. J. Wagner, see: V. Werner, Dissertation, LMU München **2015**.

B. RESULTS AND DISCUSSION

1 Preparation of Solid, Substituted Allylic Zinc Reagents and Their Reactions with Electrophiles

1.1 Introduction

Allylic organometallics are an important class of organometallic reagents owing to their enhanced reactivity compared to the corresponding alkyl, aryl, or even benzylic organometallics.³⁹ For example, allylic magnesium halides are much more reactive than all other classes of Grignard reagents.^{40,41} This behavior can be explained by the higher ionic character of the allylic C–Mg bond. Although allylic derivatives of most main-group elements have been reported,⁴² allylic zinc reagents are by far the most useful reagents in synthetic organic chemistry⁴³ since they display high reactivity and are at the same time compatible with a range of functional groups, including ester⁴⁴ or cyano functions.⁴⁵ Furthermore, allylic zinc reagents are conveniently prepared through insertion of zinc (in the form of commercially available zinc powder) into the corresponding allylic bromide.⁴⁶ Recently, we reported the preparation of solid aryl-, heteroaryl-, and benzylzinc reagents that are air stable but still display high reactivity for forming new carbon–carbon bonds.⁴⁷

³⁹ a) G. Courtois, A. Al-Arnaout, L. Miginiac, *Tetrahedron Lett.* **1985**, 26, 1027; b) M. Yasuda, K. Hirata, M. Nishino, A. Yamamoto, A. Baba, *J. Am. Chem. Soc.* **2002**, 124, 13442; c) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, 4, 3827; d) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683.

⁴⁰ a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, 93, 2207; b) D. F. Taber, J. H. Green, J. M. Geremia, *J. Org. Chem.* **1997**, 62, 9342.

⁴¹ Related solid magnesium reagents have been reported: A. Boudin, G. Cerveau, C. Chutt, R. J.P. Corriu, C. Reye, *Tetrahedron* **1989**, 45, 171.

⁴² a) Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, 102, 7107; b) M. Schlosser, O. Desponds, R. Lehmann, E. Moret, G. Rauchsvalbe, *Tetrahedron* **1993**, 49, 10175.

⁴³ a) P. Knochel, R. Singer, *Chem. Rev.* **1993**, 93, 2117; b) Y. Tamaru, A. Tanaka, K. Yasui, S. Goto, S. Tanaka, *Angew. Chem. Int. Ed.* **1995**, 34, 787; c) M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, 118, 8733; d) M. Nakamura, A. Hirai, M. Sogi, E. Nakamura, *J. Am. Chem. Soc.* **1998**, 120, 5846; e) A. Côté, A. B. Charette, *J. Am. Chem. Soc.* **2008**, 130, 2771; f) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, 1, 128; g) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, 40, 2761.

⁴⁴ a) J. Villieras, M. Rambaud, *Synthesis* **1982**, 924; b) Y. A. Dembélé, C. Belauda, P. Hitchcock, J. Villieras, *Tetrahedron: Asymmetry* **1992**, 3, 351; c) V. Nyzam, C. Belaud, F. Zammattio, J. Villieras, *Tetrahedron: Asymmetry* **1996**, 7, 1835.

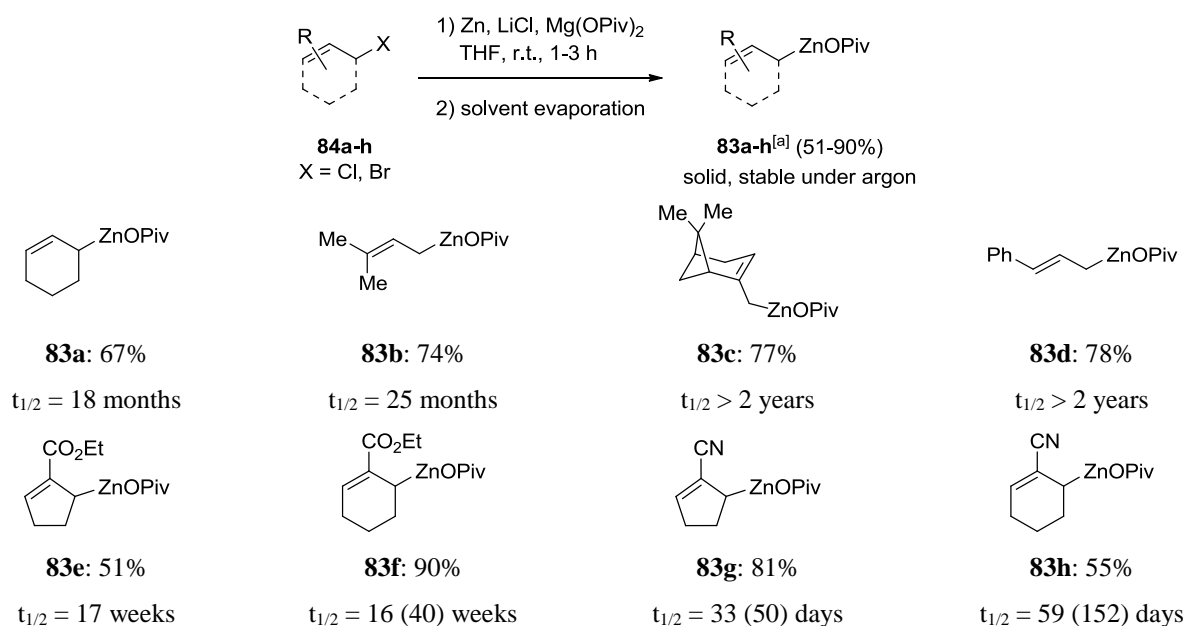
⁴⁵ a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, 129, 5376; b) M. D. Helm, P. Mayer, P. Knochel, *Chem. Commun.* **2008**, 1916; c) C. Sämann, P. Knochel, *Synthesis* **2013**, 1870.

⁴⁶ a) G. Courtois, B. Mauze, L. Miginiac, *J. Organomet. Chem.* **1974**, 72, 309; b) F. Dardoize, M. Gaudemar, *Bull. Soc. Chim. Fr.* **1976**, 9, 1561; c) M. Bellassoued, Y. Frangin, M. Gaudemar, *J. Organomet. Chem.* **1979**, 166, 1.

⁴⁷ a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, 50, 9205; *Angew. Chem.* **2011**, 123, 9372; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, 51, 9428; *Angew. Chem.* **2012**, 124, 9563; c) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, 15, 1302; d) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, 15, 5754; e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, 20, 12289.

1.2 Preparation and Application of Solid, Substituted Allylic Zinc Reagents

Consequently, we developed the synthesis of the first solid allylic zinc reagents of type **83** obtained by the insertion of zinc dust⁴⁸ in the presence of LiCl⁴⁹ and magnesium pivalate (Mg(OPiv)₂; OPiv = OCOtBu) into various allylic bromides or chlorides of type **84**. After evaporation of the solvent, solid allylic zinc derivatives are obtained as white or yellow powders. Iodometric titration⁵⁰ indicated that these zinc compounds are obtained in 51–90% yield (Scheme 25). Important functional groups such as an ester or a nitrile are tolerated in these reagents (see **83e–h**). Although these solids react rapidly with air and moisture, they are stable for an extended period of time. Thus, the allylic zinc reagents **83a–d** are thermally very stable ($t_{1/2} > 2$ years) at 25 °C as a solid under argon. The ester substituted zinc reagents (**83e–f**) have somewhat lower room temperature stability ($t_{1/2} = 16$ –17 weeks). The stability of **83f** is increased to a half-life of 40 weeks when stored at –24 °C. The nitrile-substituted allylic zinc species **83g–h** are more sensitive ($t_{1/2} = 33$ –59 d) but again, storage at –24 °C increases their stability significantly (50–152 d). The presence of LiCl and Mg(OPiv)₂ is essential for the success of the preparation of these allylic zinc reagents.⁵¹ The role of LiCl is to activate the zinc powder, whereas Mg(OPiv)₂ was found to be essential for the long term stability of the solid allylic reagents.⁵²



Scheme 25: Preparation of solid functionalized allylzinc pivalates of type **83** from the corresponding allylic halides of type **84** by using Zn, Mg(OPiv)₂ and LiCl. For the determination of the half-lives ($t_{1/2}$) see the EXPERIMENTAL PART. Values given in brackets show the half-lives when the reagents were stored at –24 °C. [a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity.

⁴⁸ Zinc dust was purchased from Sigma-Aldrich with a purity >98%, and was activated with 1,2-dibromoethane.

⁴⁹ A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; *Angew. Chem.* **2006**, *118*, 6186.

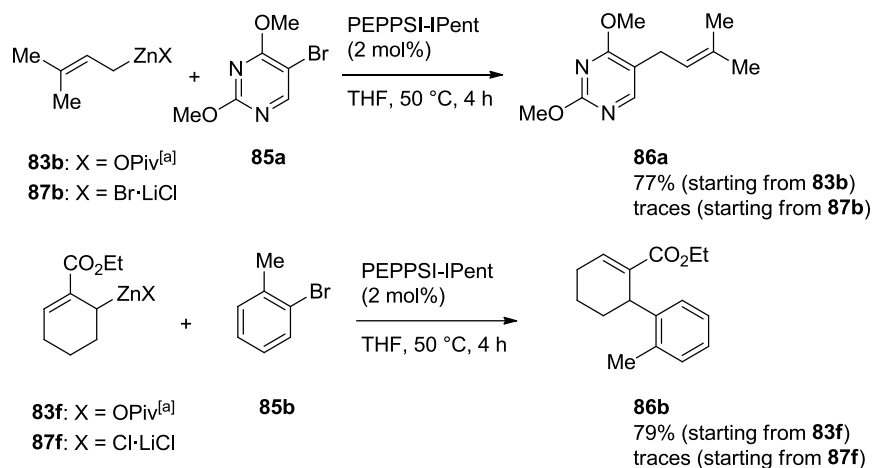
⁵⁰ See the EXPERIMENTAL PART.

⁵¹ A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706.

⁵² NMR experiments show that there is no difference between the structure "before solvent evaporation" and after redissolution of the solid reagent.

1.3 Application of Solid Allylic Zinc Pivalates in Negishi Cross-Coupling Reactions

We have first examined the reactivity of the new allylic zinc pivalates in Pd-catalyzed cross-couplings. Buchwald reported recently that prenylzinc bromide undergoes a smooth cross-coupling with various unsaturated bromides in the presence of a Pd-precatalyst and a sterically hindered phosphine ligand (CPhos).⁵³ Consequently, we examined the cross-coupling of the allylic zinc reagents of type **83** with aryl bromides in the presence of various Pd-catalysts. In our hands, PEPPSI-IPent discovered by Organ⁵⁴ gave by far the best results. Thus, prenylzinc pivalate (**83b**) undergoes a cross-coupling with bromouracil derivative **85a** in the presence of 2 mol% of PEPPSI-IPent. Interestingly, the corresponding prenylzinc bromide (**87b**) as a 0.3 M solution in THF led only to traces of the cross-coupling product (**86a**). This behavior was general and the functionalized allylic zinc reagent **83f** reacts smoothly with 2-bromotoluene (**85b**) in the presence of PEPPSI-IPent (2 mol%) producing the cross-coupling product (**86b**) in 79% yield. Again, the use of the corresponding allylic zinc chloride **87f** led only to traces of the desired product showing the importance of Mg(OPiv)₂ for such cross-couplings (Scheme 26).



Scheme 26: PEPPSI-IPent-catalyzed cross-coupling of allylic organozinc reagents (**83b,f** and **87b,f**) in THF within 4 h at 50 °C. [a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity.

The reaction scope of this Pd-catalyzed cross-coupling is quite broad and a range of unsaturated bromides provided the cross-coupling products (**86c–g**) in 69–79% yield (Table 1).⁵⁵ Thus, the cross-coupling of zinc pivalate **83a** using electron poor 1-bromo-3-(trifluoromethyl)benzene (**85c**) and 2 mol% of PEPPSI-IPent proceeds within 4 h at 50 °C and provides the cross-coupling product (**86c**) in 69% yield (entry 1). Remarkably, the electron rich aryl bromides **85b** and **85d** also undergo the cross-coupling reaction to afford the expected products **86d–e** (70–71% yield, entries 2–3). Similarly, the myrtenylzinc species **83c** reacts with 1-bromo-3-fluorobenzene (**85e**) providing after 4 h at 50 °C only the linear regioisomer (**86f**) in 77% yield (entry 4). Also heteroaromatic bromides such as

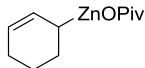
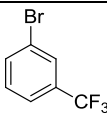
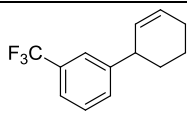
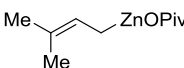
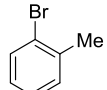
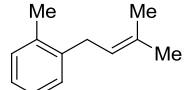
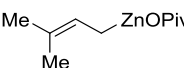
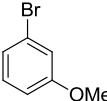
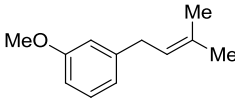
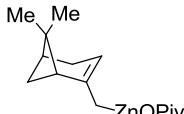
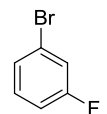
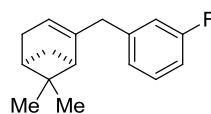
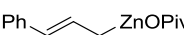
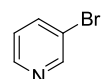
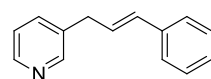
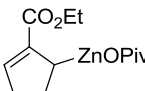
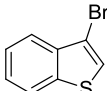
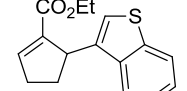
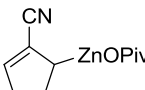
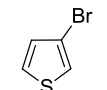
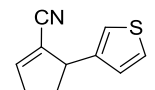
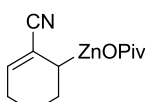
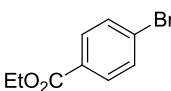
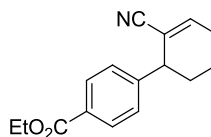
⁵³ Y. Yang, T. J. L. Mustard, P. H.-Y. Cheong, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, 52, 14098.

⁵⁴ C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, 12, 4743.

⁵⁵ Following the same procedure, the cross-coupling of allylzinc reagent **83b** with β -bromostyrene led to the desired *E*-1,4-diene in 81% yield (>99% *E*).

3-bromopyridin (**85f**) was readily allylated with cinnamylzinc pivalate (**83d**) leading to the functionalized heteroaromatic product (**86g**) in 72% yield (entry 5). By following the same procedure, ester- and cyano-functionalized organozinc pivalates (**83e–h**) were converted into the corresponding polyfunctional cross-coupling products (**86h–j**) in 75–90% yield (entries 6–8).

Table 1: PEPPSI-IPent-catalyzed cross-coupling of allylic organozinc pivalates of type **83** in THF within 4 h at 50 °C

Entry	Zinc Reagent ^[a]	Electrophile ^[b]	Product ^[c]
1	 83a	 85c	 86c : 69%
2	 83b	 85b	 86d : 70%
3	 83b	 85d	 86e : 71%
4	 83c	 85e	 86f : 77%
5	 83d	 85f	 86g : 72%
6	 83e	 85g	 86h : 75%
7	 83g	 85h	 86i : 90%
8	 83h	 85i	 86j : 88%

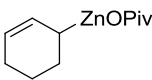
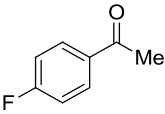
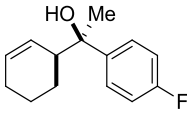
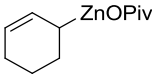
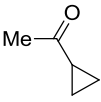
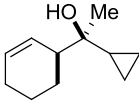
[a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity. [b] 0.80 equiv. of electrophile were used.

[c] Yields refer to analytically pure products.

1.4 Diastereoselective Addition of Allylic Zinc Pivalates to Aldehydes and Ketones

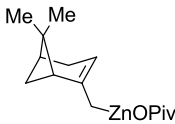
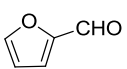
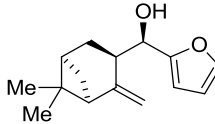
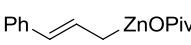
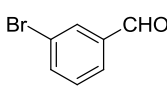
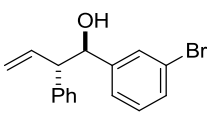
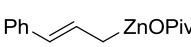
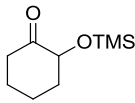
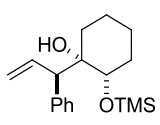
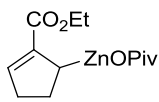
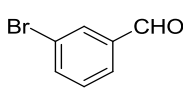
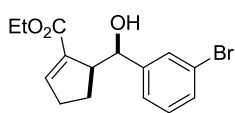
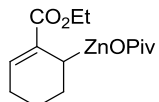
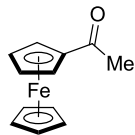
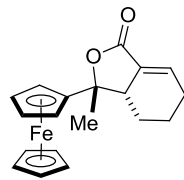
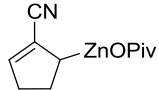
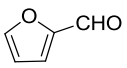
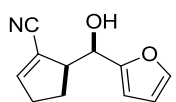
In addition, the solid allylic zinc reagents of type **83** react as previously reported allylic zinc halides⁵⁶ with electrophiles such as carbonyl derivatives or acid chlorides with complete regioselectivity (formation of the new carbon-carbon bond from the most substituted end of the allylic system) and very high diastereoselectivity as shown in Table 2 and Scheme 27. Thus, the cyclohex-2-en-1-ylzinc reagent **83a** (1.0 equiv) in THF adds to various methyl ketones^{45a} (0.8 equiv) leading to the corresponding homoallylic alcohols (**89a–b**) in 89–92% yield and d.r. > 99:1 (Table 2, entries 1–2). The 2,3-disubstituted allylic zinc species **83c** reacts with furfural (**88c**) with complete regio- and diastereoselectivity leading to the alcohol **89c** in 89% yield (entry 3). Cinnamylzinc pivalate (**83d**) displays a similar behavior leading to the *anti*-alcohol (**89d**) in 86% yield and d.r. > 99:1. This zinc reagent allows the stereo control of three contiguous centers and its addition to 2-trimethylsilyloxy cyclohexanone (**88e**) provides the alcohol **89e** in 80% yield (d.r. = 95:5; entry 5). The structure of alcohol **89e** was confirmed by X-ray analysis.⁵⁷ The solid functionalized zinc reagent **83e** reacts smoothly with 3-bromobenzaldehyde (**88f**) furnishing the secondary alcohol **89f** in 91% (d.r. = 97:3; entry 6). Finally, the functionalized zinc reagents (**83f,g**) bearing an ester or cyano function in position 2 react with the ferrocenyl methyl ketone (**88g**) and furfural (**88c**) furnishing the products **89g,h** in 91–92% yield and d.r. > 99:1 (entries 7–8). In the case of the addition of the allylzinc pivalate **83f** to **88g** a spontaneous lactonization was observed leading to the bicyclic product **89g** (entry 7).⁵⁷

Table 2: Diastereoselective preparation of homoallylic alcohols of type **89** using solid, functionalized allylzinc pivalates of type **83**

Entry	Zinc Reagent ^[a]	Electrophile	Product ^[b]
1	 83a	 88a	 89a : 89% d.r. > 99:1
2	 83a	 88b	 89b : 92% d.r. = 94:6

⁵⁶ a) S. E. Denmark, E. J. Weber, *Helv. Chim. Acta.* **1983**, 66, 1655; b) Y. Yamamoto, *Acc. Chem. Res.* **1987**, 20, 243.

⁵⁷ CCDC 1061748 (**89e**) and 1061747 (**89g**) contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

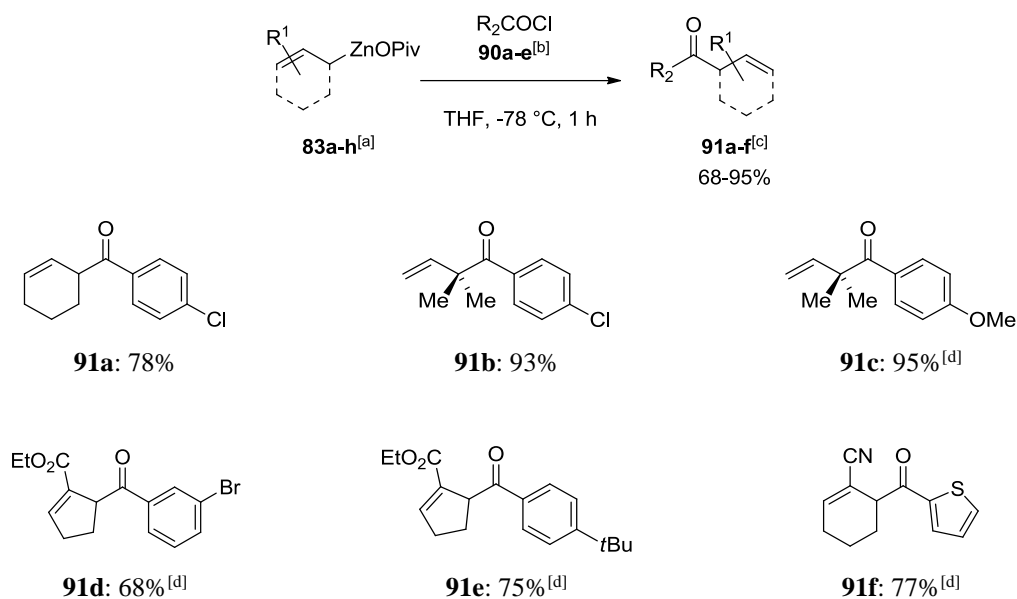
3	 83c	 88c	 89c : 89% d.r. > 99:1
4	 83d	 88d	 89d : 86% d.r. > 99:1
5	 83d	 88e	 89e : 80% d.r. = 95:5
6	 83e	 88f	 89f : 91% d.r. = 97:3
7	 83f	 88g	 89g : 92% d.r. > 99:1
8	 83g	 88c	 89h : 91% d.r. > 99:1

Reaction conditions: 0.80 equiv. of electrophile, THF, -78°C , 1 h. [a] Complexed $\text{Mg}(\text{OPiv})\text{X}$ ($\text{X}=\text{Cl}$, Br) and LiCl are omitted for clarity. [b] Yields refer to analytically pure products; The d.r. was determined by NMR- and/or GC analysis of the crude product.

1.5 Acylation of Allylic Zinc Pivalates Using Acid Chlorides

Furthermore, the method was also applicable to the synthesis of various β,γ -unsaturated ketones of type **91** by addition of the solid functionalized allylzinc pivalates of type **83** to acid chlorides in the absence of any transition metal catalyst (Scheme 27). Thus, the allylic reagents **83a** and **83b** react in THF under very mild conditions (1 h, -78°C) with 4-chlorobenzoyl chloride (**90a**) and 4-methoxybenzoyl chloride

(**90b**) to give the β,γ -unsaturated ketones **91a-c** in 78–95% yield without any trace of the α,β -unsaturated isomers. Interestingly, the competitive formation of a mixed anhydride by the reaction of the pivalate anion (PivO^-) with the acyl chloride was not observed.^{27e} Thus, starting from 3-bromobenzoyl chloride (**90c**) or 4-(*tert*-butyl)benzoyl chloride (**90d**) the corresponding β,γ -unsaturated ketones **91d-e** were obtained in 68–75% yield using the functionalized organozinc pivalate **83e**. Furthermore, the addition of the solid cyano-functionalized zinc reagent **83f** to thiophene-2-carbonyl chloride (**90e**) furnished selectively the corresponding ketone **91f** in 77% yield.



Scheme 27: Reaction of the solid functionalized allylzinc pivalates (**83a-h**) with acid chlorides (**90a-e**). [a] Complexed $\text{Mg}(\text{OPiv})\text{X}$ ($\text{X}=\text{Cl}, \text{Br}$) and LiCl are omitted for clarity. [b] 0.80 equiv. of electrophile were used. [c] Yields refer to analytically pure products. [d] The reaction mixture was warmed to r.t. overnight.

2 Preparation and Application of Solid, Salt Stabilized Amide Enolates

2.1 Introduction

Metal enolates are an important class of reagents for organic synthesis⁵⁸ and in recent years derivatives of Li,⁵⁹ Mg,⁶⁰ B,⁶¹ and Si⁶² have found extensive applications in the stereoselective elaboration of aldol products. Furthermore, the arylation of enolates is an important transformation for which alkali metal- or Si- enolates have been used.⁶³ *In situ* generated Zinc enolates known in the literature as Reformatsky reagents have also proved their utility in Pd-catalyzed arylations.⁶⁴ However, in this respect Reformatsky reagents did not find extensive applications as their lower chemical and thermal stability compared to silyl enol ethers is a major drawback. As shown in Chapter 1 we have found that the presence of Mg(OPiv)₂ strongly enhanced the air and moisture stability of solid allylic zinc reagents which have extended half-lives under argon up to 2 years. Hence, we envisioned a general method with Mg(OPiv)₂ as an additive for Reformatsky reagents allowing the preparation of solid zinc enolates of high thermal and moisture stability.

2.2 Optimization of the Preparation of Solid Reformatsky Reagents

First, we examined the stability of different organozinc enolates upon storage in a sealed flask under argon. Thus, the metalation of *tert*-butyl acetate and *N,N*-dimethylacetamide using TMPZnCl·LiCl (**19**) in the presence of Mg(OPiv)₂ led to colorless solids, which showed a poor stability under argon (11% and 54% active species left after 2 weeks under argon) (Table 3, entries 1 and 2). An improved stability of the zinc enolate was found starting from 1-morpholinoethanone where the zinc enolate still showed 97% of the initial activity after storage under argon for four weeks (entry 3). Furthermore, it was found that the morphonyl amide containing zinc enolate showed an improved stability when exposed to air as

⁵⁸ a) T. Mukaiyama, *Pure Appl. Chem.* **1983**, 55, 1749; b) R. Mahrwald, B. Schetter, *Angew. Chem. Int. Ed.* **2006**, 45, 7506.

⁵⁹ D. Seebach, *Angew. Chem. Int. Ed.* **1988**, 27, 1624.

⁶⁰ E. R. Hurley, X. He, S. N. Brown, K. W. Henderson, *J. Am. Chem. Soc.* **2009**, 131, 6056.

⁶¹ a) S. Masamune, W. Choy, B. Imperiali, *J. Am. Chem. Soc.* **1981**, 103, 1566; b) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, 103, 3099; c) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, 103, 2127.

⁶² a) G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **1968**, 90, 4462; b) E. M. Carreira, R. A. Singer, W. Lee, *J. Am. Chem. Soc.* **1994**, 116, 8837; c) Takahiko Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566.

⁶³ a) A. A. Millard, M. W. Rathke, *J. Am. Chem. Soc.* **1977**, 99, 4833; b) I. Kuwajima, H. Urabe, *J. Am. Chem. Soc.* **1982**, 104, 6831; c) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, 119, 12382; d) W. Cabri, I. Candiani, A. Bedeschi, S. Penco, R. Santi, *J. Org. Chem.* **1992**, 57, 1481; e) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 1261; f) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, 36, 234; g) C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, 49, 676.

⁶⁴ a) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 11176; b) E. Bentz, M. G. Moloney, S. M. Westaway, *Tetrahedron Lett.* **2004**, 45, 7395; c) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, 128, 4976; d) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, 110, 1082.

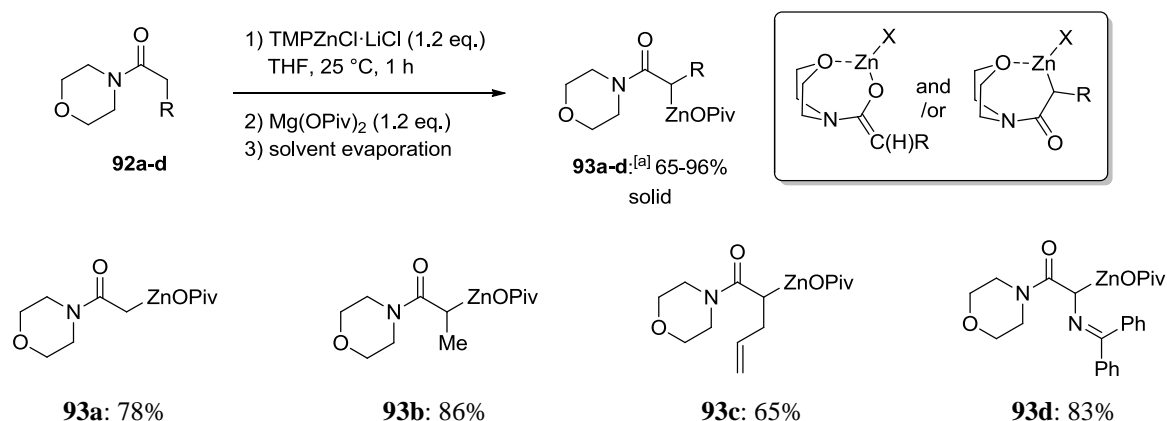
85% are retained after 2 h in air (entry 4). The corresponding Mg-free organozinc halides prepared by metalation using $\text{TMPZnCl} \cdot \text{LiCl}$ (**19**) or by TMPLi followed by transmetalation with Zn(OPiv)_2 retained after 2 h in air only 59% and 36% respectively (entries 5 and 6). When MgCl_2 was added before the transmetalation with Zn(OPiv)_2 the air stability was increased (79% after 2 h air exposure, entry 7).

Table 3: Optimization of the preparation of acetyl enolates

Entry	Conditions	R	Treatment	Activity [%]
1	$\text{TMPZnCl} \cdot \text{LiCl} / \text{Mg(OPiv)}_2$	<i>t</i> BuO	argon (2 weeks)	11
2	$\text{TMPZnCl} \cdot \text{LiCl} / \text{Mg(OPiv)}_2$	Me_2N	argon (2 weeks)	54
3	$\text{TMPZnCl} \cdot \text{LiCl} / \text{Mg(OPiv)}_2$		argon (4 weeks)	97
4	$\text{TMPZnCl} \cdot \text{LiCl} / \text{Mg(OPiv)}_2$		air (2 h)	85
5	$\text{TMPZnCl} \cdot \text{LiCl}$		air (2 h)	59
6	$\text{TMPLi} / \text{Zn(OPiv)}_2$		air (2 h)	36
7	$\text{TMPLi} / \text{MgCl}_2, \text{Zn(OPiv)}_2$		air (2 h)	79

2.3 Preparation of Solid Amide Enolates and Their Application in Cross-Couplings, Allylations, and Carbonyl Additions

With these optimized conditions in hand, the treatment of various morphonyl amides (**92a-d**) with $\text{TMPZnCl} \cdot \text{LiCl}$ (**19**) in the presence of Mg(OPiv)_2 at 25 °C for 15 min to 1 h produced after solvent evaporation the solid zinc enolates **93a-d** as easy-to-handle white or yellow powders (Scheme 28). These reagents show an exceptional stability and can be stored under argon at room temperature for several months without significant loss of activity. The use of morphonyl amides led to much more robust compounds, which preserved their activity even after contact with air. Thus, zinc enolate **93b** preserved 72% of its activity after 1 h on air. Importantly, the zinc compound can now be weighed in air (94% of the active zinc species **93b** is titrated after 10 min in air).



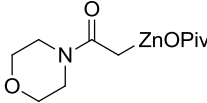
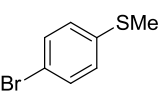
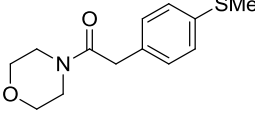
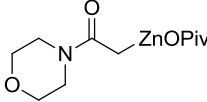
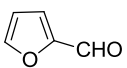
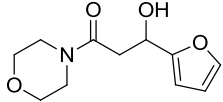
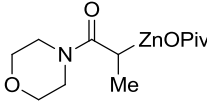
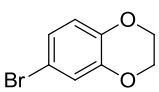
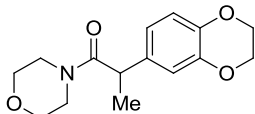
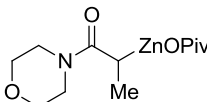
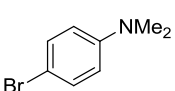
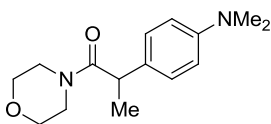
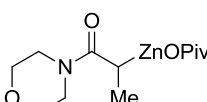
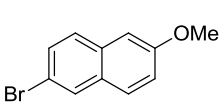
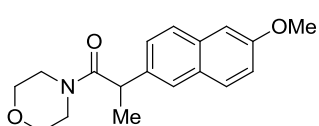
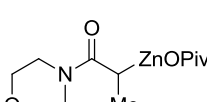
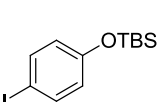
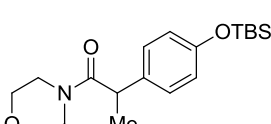
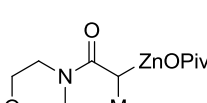

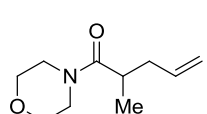
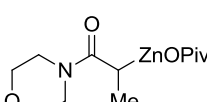
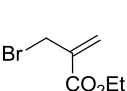
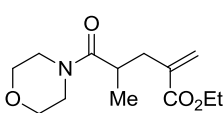
Scheme 28: Preparation of solid zinc amide enolates of type **93** from the corresponding morphonyl amides of type **92** by using $\text{TMPZnCl} \cdot \text{LiCl}$ (**19**) in the presence of $\text{Mg}(\text{OPiv})_2$. [a] $\text{X} = \text{Cl} \cdot \text{Mg}(\text{OPiv})_2 \cdot \text{LiCl}$.

Furthermore, these solid zinc enolates proved to be excellent nucleophiles in Negishi cross-couplings, allylations and aldehyde additions.⁶⁵ Thus, zinc reagent **93a** reacts with (4-bromophenyl)(methyl)sulfane (**85j**) using 2 mol% $\text{Pd}(\text{OAc})_2$ and 4 mol% DavePhos⁶⁶ after 18 h at 25 °C and with furfural (**88c**) without the need of an external catalyst to the desired products **94a** and **95a** in 99% yield (Table 4, entries 1 and 2). Zinc enolate **93b** was used in a range of palladium catalyzed cross-coupling reactions with aryl bromides **85k-l** to the corresponding α -arylated amides **94b-c** in 97–99% yield (entries 3–4). Furthermore, the \pm -naproxen derivative **94d** was successfully prepared by the $\text{Pd}(\text{OAc})_2$ /DavePhos catalyzed cross-coupling of zinc enolate **93b** with 2-bromo-6-methoxynaphthalene (**85m**) in 99% yield (entry 5). Aryl iodide **96a** also underwent a smooth coupling with amide enolate **93b** and furnished the α -arylated amide **94e** in 90% yield (entry 6). The reaction of zinc enolate **93b** with the allylic bromides **97a,b** in the presence of 10 mol% $\text{CuCN} \cdot \text{LiCl}$ led to the allylation products **98a,b** in 99% and 97% yield (entries 7–8).

⁶⁵ a) J. Cossy, A. de Filippis, D. G. Pardo, *Org. Lett.* **2003**, 5, 3037; b) J. Cossy, A. de Filippis, D. G. Pardo, *Synlett* **2003**, 2171; c) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 11176; d) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, 125, 11177; e) A. de Filippis, D. G. Pardo, J. Cossy, *Tetrahedron*, **2004**, 60, 9757; f) E. Bentz, M. G. Moloney, S. M. Westaway, *Tetrahedron Lett.* **2004**, 45, 7395; g) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, 128, 4976; h) G. Satyanarayana, M. E. Maier, *Tetrahedron* **2008**, 64, 356; i) S. L. McDonald, Q. Wang, *Chem. Commun.* **2014**, 50, 2535; j) B. Wong, X. Linghu, J. J. Crawford, J. Drobnick, W. Lee, H. Zhang, *Tetrahedron* **2014**, 70, 1508.

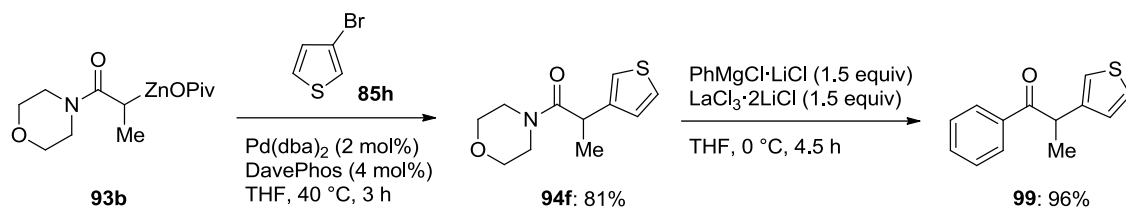
⁶⁶ a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, 41, 1461; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, 2, 27.

Table 4: Application of solid pivaloxy zinc amide enolates of type **93** in cross-couplings, allylations and carbonyl additions

Entry	Zinc Reagent ^[a]	Electrophile	Product ^[b]
1	 93a	 85j	 94a: 99%^[c]
2	 93a	 88c	 95a: 99%
3	 93b	 85k	 94b: 99%^[c]
4	 93b	 85l	 94c: 97%^[c]
5	 93b	 85m	 94d: 99%^[c]
6	 93b	 96a	 94e: 90%^[c]
7	 93b	 97a	 98a: 99%^[d]
8	 93b	 97b	 98b: 97%^[d]

[a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity. [b] Yields refer to analytically pure products. [c] 2 mol% Pd(OAc)₂ and 4 mol% DavePhos were used as the catalytic system. [d] 10 mol% CuCN·LiCl were used as a catalyst.

Another advantage of the morpholineamide moiety is the facile substitution to the corresponding ketones.⁶⁷ Thus, the α -arylated amide **94f** which was prepared by cross-coupling of organozinc pivalate **93b** and 3-bromothiophene (**85h**) was reacted with PhMgCl·LiCl in the presence of stoichiometric amounts of LaCl₃·2LiCl⁶⁸ to form ketone **99** after 4.5 h at 0 °C in 96% yield (Scheme 29).



Scheme 29: Preparation of α -arylated amide **94f** and subsequent substitution of the morpholineamide using PhMgCl·LiCl and LaCl₃·2LiCl.

⁶⁷ a) M. Kurosu, Y. Kishi, *Tetrahedron Lett.* **1998**, 39, 4793; b) C. Douat, A. Heitz, J. Martinez, J.-A. Fehrentz, *Tetrahedron Lett.* **2000**, 41, 37; c) M. Badioli, R. Ballini, M. Bartolacci, G. Bosica, E. Torregiani, E. Marcantoni, *J. Org. Chem.* **2002**, 67, 8938; d) A. R. Jeon, M. E. Kim, J. K. Park, W. K. Shin, D. K. An, *Tetrahedron*, **2014**, 70, 4420.

⁶⁸ A. Krasovskiy, F. Kopp, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, 45, 497.

3 Scalable Preparation of Functionalized (Hetero-)Arylzinc Pivalates

3.1 Introduction

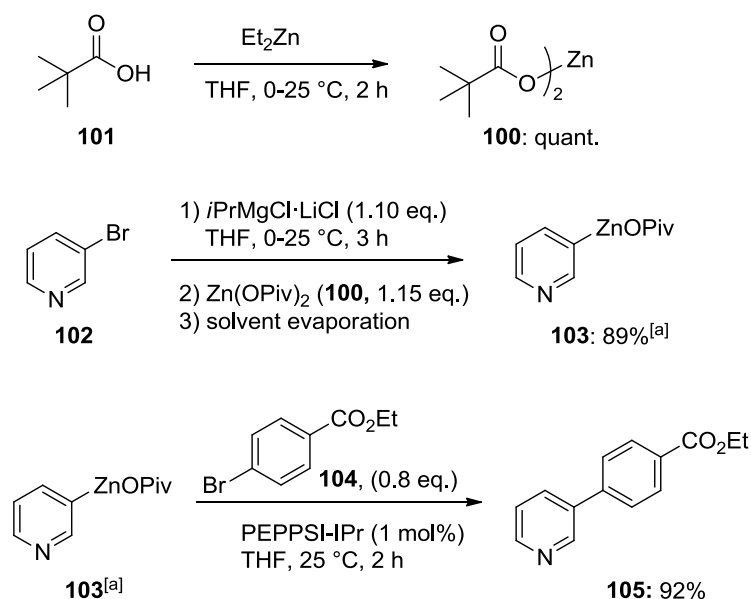
For many years, aromatic and heterocyclic boron and zinc organometallics have been the most important reagents for sp^2 - sp^2 cross-coupling reactions due to their high compatibility with a broad variety of functional groups.⁶⁹ However, the limited stability towards air and moisture represents a serious drawback of organozinc reagents for their practical use in the laboratory and for industrial applications. On the other hand, the lower reactivity and transmetalation ability of boronic derivatives as well as toxicity issues makes the availability of bench-stable organozinc reagents highly desirable. To overcome this problem, we recently developed a method for the preparation of aryl and heteroaryl zinc pivalates, which are easy-to-handle solids with exceptional stability when exposed to air (see INTRODUCTION 3). These reagents can be weighed out on the benchtop and have the potential for extended shelf life. Thus, they could represent highly efficient reagents for the functionalization of various complex molecules, and hence represent valuable building blocks to be used by both synthetic and medicinal chemists. In order to examine the performance of the organozinc pivalates in high throughput screenings a feasible preparation in gram-scale was developed.

3.2 Scalable Protocol for the Preparation of Functionalized Organozinc Pivalates

The preparation of zinc pivalate (**100**) was performed on a 53 mmol scale from pivalic acid (**101**) and diethylzinc (Scheme 30). After stirring in THF for 2 h at room temperature zinc pivalate was obtained as a puffy amorphous white solid in quantitative yield. The resulting salt was added to the subsequent reaction of 3-bromopyridine (**102**) with *i*PrMgCl·LiCl after 3 h at 25 °C in THF. After solvent evaporation pyridin-3-ylzinc pivalate (**103**) was produced in 89% yield. Cross-coupling of the reagent **103** with ethyl 4-bromobenzoate (**104**) using PEPPSI-IPr (THF, 25 °C, 2 h) furnished ethyl 4-(pyridin-3-yl)benzoate (**105**) in 92% yield (5.52 g) on a 26 mmol scale.⁷⁰

⁶⁹ Organozinc compounds see: a) P. Knochel, J. Almena, P. Jones, *Tetrahedron* **1998**, *54*, 8275; b) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; d) P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, pp. 251; e) A. Lemire, A. Côté, M. K. Janes, A. B. Charette, *Aldrichimica Acta* **2009**, *42*, 71; Boron organometallics see: f) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466; g) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961; h) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758; i) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972; j) A. Suzuki, *Pure & Appl. Chem.* **1985**, *57*, 1749; k) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; l) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302; m) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.

⁷⁰ The detailed procedure for these transformations can be found in the EXPERIMENTAL PART.



Scheme 30: Scale-up preparation of zinc pivalate (**100**) and pyridin-3-ylzinc pivalate (**103**). Subsequent cross-coupling with 4-bromobenzoate (**104**) using PEPPSI-IPr to ethyl 4-(pyridin-3-yl)benzoate (**105**). [a] Complexed $\text{Mg}(\text{OPiv})\text{Br}$ and LiCl are omitted for clarity.

3.3 Preparation of a Set of 17 Polyfunctional Aryl, Benzyl, and Heteroarylzinc Pivalates

With this optimized preparation protocol in hands, various polyfunctional benzylic, aryl-, and heteroarylzinc pivalates **106–122** were prepared on a 7.0 mmol scale and stored in sealed/inerted ampules containing approximately 0.125 mmol of each reagent (Figure 3). The protocol was slightly changed for compounds **109**, **110**, **114**, **115**, **116**, **118** which were prepared by magnesium insertion followed by transmetalation with $\text{Zn}(\text{OPiv})_2$ (see EXPERIMENTAL PART). Furthermore, compound **119** was prepared *via* metalation using $\text{TMPMgCl}\cdot\text{LiCl}$ (**17**) followed by the addition of solid $\text{Zn}(\text{OPiv})_2$ whereas reagents **107**, **112**, **120**, **122** were prepared using directly the base TMPZnOPiv (**27**). The preparation of compound **106** on a 70 mmol scale led to the desired product in a slightly increased yield (77% and 71% on 7.0 mmol scale). However, performing the reaction on a 70 mmol scale led in other cases to significantly lower yields. For instance, the preparation of reagent **109** was achieved in 27% yield on 70 mmol and in 83% on 7.0 mmol scale.

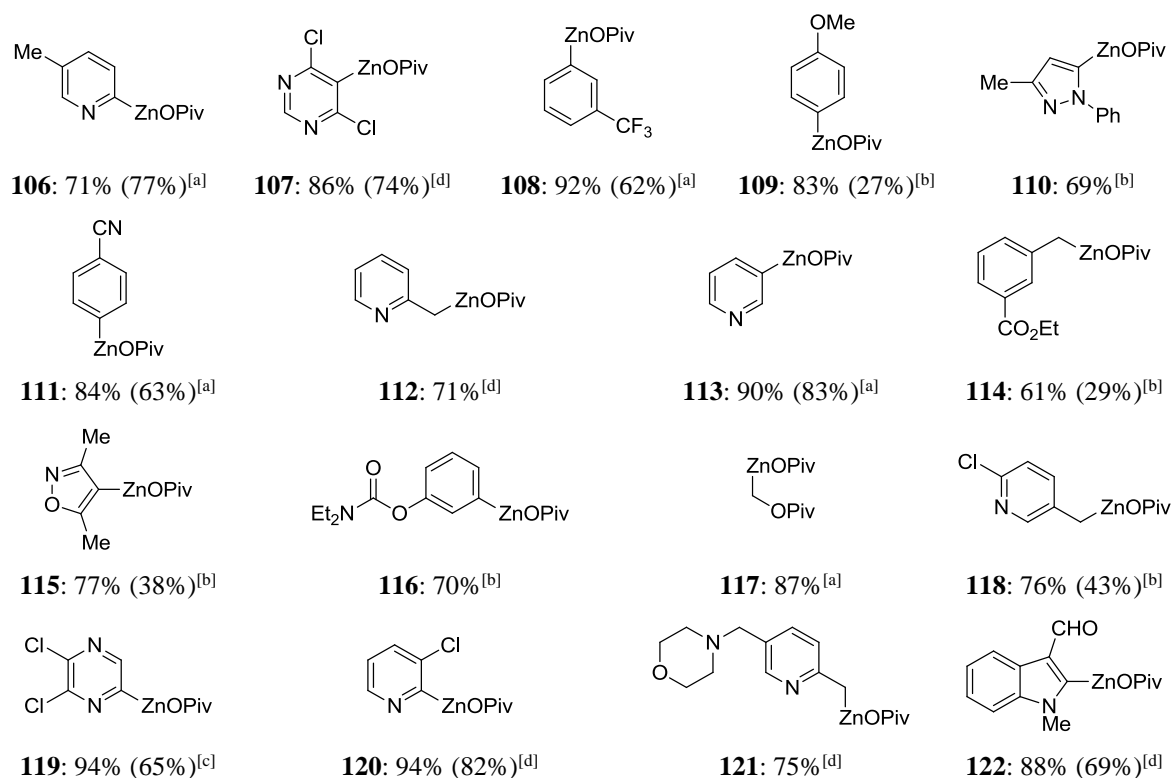


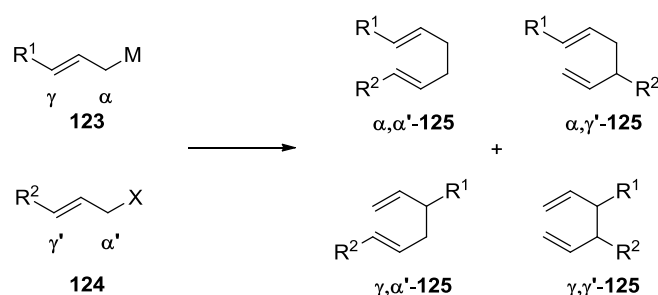
Figure 3: Set of 17 polyfunctional aryl, benzyl, and heteroarylzinc pivalates prepared on a 7.0 mmol scale (values in parentheses represent the yield on a 70 mmol scale). Complexed $\text{Mg}(\text{OPiv})\text{X}$ ($\text{X}=\text{Cl}, \text{Br}, \text{I}$) and LiCl are omitted for clarity. [a] Prepared *via* halogen-magnesium exchange using $i\text{PrMgCl}\cdot\text{LiCl}$ followed by transmetalation with $\text{Zn}(\text{OPiv})_2$. [b] Prepared *via* magnesium insertion using magnesium turnings and LiCl followed by transmetalation with $\text{Zn}(\text{OPiv})_2$. [c] Prepared *via* metalation using $\text{TMPMgCl}\cdot\text{LiCl}$ (**17**) followed by transmetalation with $\text{Zn}(\text{OPiv})_2$. [d] Prepared *via* metalation using TMPZnOPiv (**27**).

This set of reagents could be used for high throughput screenings in medicinal chemistry, e.g., in a late stage functionalization of drugs *via* palladium catalyzed Negishi cross-couplings. The feasible handling of the air-stable powders and the tolerance of technical solvents as well as the excellent shelf-life of these compounds could make the organozinc pivalates a valuable tool in synthetic chemistry.

4 Regioselective Transition-Metal-Free Allyl–Allyl Cross-Couplings

4.1 Introduction

Transition-metal-catalyzed cross-couplings represent a major tool for forming new carbon–carbon bonds.⁷¹ Although Pd-⁷² and Ni-⁷³ catalyzed cross-couplings have found numerous applications, the search for alternative transition metal catalysts such as Fe and Co salts⁷⁴ have become increasingly important owing to economical and toxicity issues. Alternatively, the performance of cross-couplings without transition metals as reported by Hayashi,⁷⁵ Uchiyama,⁷⁶ and others⁷⁷ opens new perspectives for sustainable C–C bond formations. In this respect, allylic organometallics represent a promising class of organometallic reagents since the carbon–metal bond in these compounds is typically highly polarized and therefore highly reactive. Thus, the cross-coupling between 3-substituted allylic organometallics of type **123** with 3-substituted allylic halides of type **124** may provide up to four regioisomeric coupling products of type **125** (Scheme 31).



Scheme 31: Cross-coupling of allylic organometallic **123** with allylic halide **124** leading to four regioisomeric coupling products of type **125**.

In pioneering work, Y. Yamamoto and co-workers achieved a regioselective head-to-tail (γ,α') cross-coupling using allylic boronate complexes and allylic halides.⁷⁸ More recently, several transition-metal-

⁷¹ a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, A. de Meijere), 2nd ed. Wiley-VCH, Weinheim, **2004**; b) *Organotransition Metal Chemistry* (Ed.: J. F. Hartwig), University Science Books, Sausalito, **2010**.

⁷² *Palladium Reagents and Catalysts: New Perspectives for the 21st Century* (Ed.: J. Tsuji), Wiley, Weinheim, **2004**.

⁷³ R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417.

⁷⁴ a) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2002**, *41*, 4137; b) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297; c) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

⁷⁵ E. Shirakawa, Y. Hayashi, K. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, S. Masui, T. Hayashi, *Angew. Chem. Int. Ed.* **2012**, *51*, 218; *Angew. Chem.* **2012**, *124*, 222.

⁷⁶ a) H. Minami, X. Wang, C. Wang, M. Uchiyama, *Eur. J. Org. Chem.* **2013**, 7891; b) H. Minami, T. Saito, C. Wang, M. Uchiyama, *Angew. Chem. Int. Ed.* **2015**, *54*, 4665; *Angew. Chem.* **2015**, *127*, 4748.

⁷⁷ a) F. Ding, R. William, F. Wang, X.-W. Liu, *Chem. Commun.* **2012**, *48*, 8709; b) N. Uchiyama, E. Shirakawa, T. Hayashi, *Chem. Commun.* **2013**, *49*, 364; c) Q. Chen, X. Mollat du Jourdin, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 4958; d) Q. Chen, T. León, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 8746; *Angew. Chem.* **2014**, *126*, 8891; e) P. Quinio, D. Sustac Roman, T. León, S. William, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 4396.

⁷⁸ Y. Yamamoto, K. Maruyama, *J. Am. Chem. Soc.* **1978**, *100*, 6282.

catalyzed allyl–allyl cross-couplings have been reported by the groups of Morken⁷⁹ and others.⁸⁰ H. Yamamoto and co-workers have shown that both α - and γ -selective allyl–allyl cross-couplings can be accomplished using either allylic barium halides⁸¹ or allylic magnesium halides.⁸²

Recently, we have described convenient mild preparations of functionalized allylic zinc reagents and demonstrated their utility in synthesis.⁸³ In contrast to most reactive allylic organometallics, these allylic zinc reagents tolerate various functional groups. Therefore, we envisioned that the allyl–allyl cross-coupling between such functionalized allylic zinc reagents and substituted allylic halides may provide access to a broad range of functionalized 1,5-dienes of type **125**.

4.2 Preparation of Allylzinc Halides and Reaction with Allylic Halides

In preliminary experiments, we examined the cross-coupling of prenylzinc bromide (**123a**), which was generated by the insertion of zinc dust in the presence of LiCl in THF (1 h, 25 °C, 72% yield), with (*E*)-1-bromonon-2-ene (**124a**), at various temperatures and in several solvent mixtures (Table 5). Thus, the addition of the zinc species **123a** to the allylic bromide **124a** in THF at room temperature led to a mixture of all four regioisomers ($\alpha,\alpha'/\alpha,\gamma'/\gamma,\alpha'/\gamma,\gamma'$ =33:25:35:7; entry 1). Selectivity in favor of the α,α' -isomer was obtained by lowering the reaction temperature to –10 °C and –40 °C (57% and 88% of the α,α' -isomer were obtained, respectively; entries 2 and 3). This α,α' -regioselectivity was not further improved as we found that the addition of various cosolvents leads to a shift to the regioisomer γ,α' -**125a**.

⁷⁹ a) L. A. Brozek, M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2011**, *133*, 16778; b) H. Le, A. Batten, J. P. Morken, *Org. Lett.* **2014**, *16*, 2096; c) M. J. Ardolino, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 7092; d) M. J. Ardolino, J. P. Morken, *Tetrahedron* **2015**, *71*, 6409.

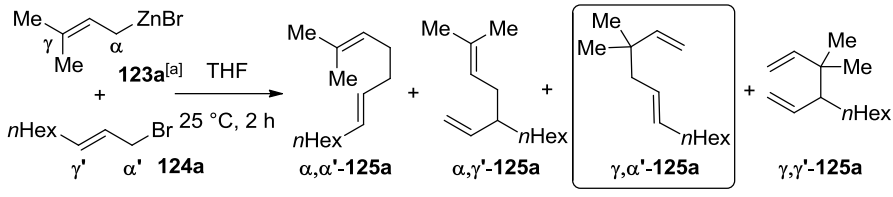
⁸⁰ For transition metal catalyzed allyl–allyl cross-couplings, see a) K. Sekiya, E. Nakamura, *Tetrahedron Lett.* **1988**, *29*, 5155; b) E. F. Flegeau, U. Schneider, S. Kobayashi, *Chem. Eur. J.* **2009**, *15*, 12247; c) V. Hornillos, M. Pérez, M. Fañanás-Mastral, B. L. Feringa, *J. Am. Chem. Soc.* **2013**, *135*, 2140; d) Q. Yuan, K. Yao, D. Liu, W. Zhang, *Chem. Commun.* **2015**, *51*, 11834; e) K. Semba, N. Bessho, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.* **2014**, *53*, 9007; *Angew. Chem.* **2014**, *126*, 9153.

For transition metal free allyl–allyl cross-couplings, see f) C. Prévost, P. Miginiac, L. Miginiac-Groizeleau, *Bull. Soc. Chim. Fr.* **1964**, 2485; g) Y. Yamamoto, H. Yatagai, K. Maruyama, *J. Chem. Soc. Chem. Commun.* **1979**, 157; h) Y. Yamamoto, H. Yatagai, K. Maruyama, *J. Am. Chem. Soc.* **1981**, *103*, 1969; i) A. Hosomi, T. Imai, M. Endo, H. Sakurai, *J. Organomet. Chem.* **1985**, *285*, 95; j) V. Calo, L. Lopez, G. Pesce, *J. Chem. Soc. Perkin Trans. I* **1988**, 1301; k) S. Araki, T. Shimizu, S.-J. Jin, Y. Butsugan, *J. Chem. Soc. Chem. Commun.* **1991**, 824; l) S. Araki, S.-J. Jin, Y. Butsugan, *J. Chem. Soc. Perkin Trans. I* **1995**, 549.

⁸¹ a) A. Yanagisawa, H. Hibino, S. Habaue, Y. Hisada, K. Yasue, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1263; b) A. Yanagisawa, K. Yasue, H. Yamamoto, *Synlett* **1996**, 842.

⁸² A. Yanagisawa, H. Hibino, N. Nomura, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 5879.

⁸³ a) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376; b) M. D. Helm, P. Mayer, P. Knochel, *Chem. Commun.* **2008**, 1916; c) C. Sämann, P. Knochel, *Synthesis* **2013**, 1870.

Table 5: Optimization of the conditions for the allyl-allyl cross-coupling


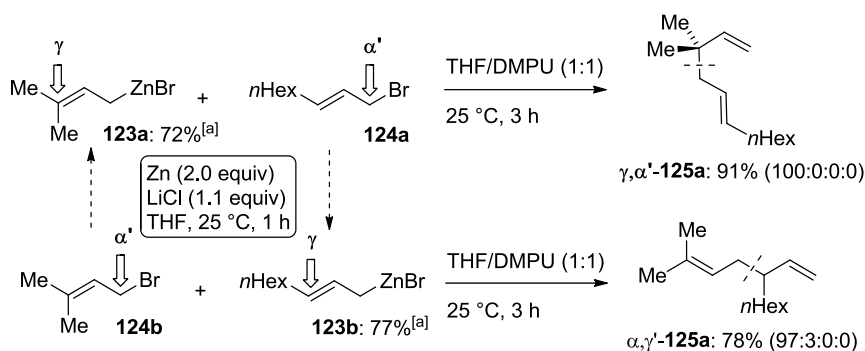
Entry	Temp. [°C]	Cosolvent ^[b]	α,α'	α,γ'	γ,α'	γ,γ'	Yield ^[c] [%]
1	25	none	33	25	35	7	75
2	-10	none	57	27	10	6	65
3	-40	none	88	8	4	0	61
4	25	toluene	4	5	89	2	94
5	25	<i>n</i> -hexane	16	2	82	0	82
6	25	1,4-dioxane	5	10	81	4	92
7	25	DMSO	0	5	91	4	100
8	25	NMP	0	5	95	0	100
9	25	DMPU	0	0	100	0	100 (91)^[d]
10	25	DMPU ^[e]	10	15	71	4	100

[a] LiCl is omitted for clarity. [b] A 1:1 mixture with THF was used. [c] Determined by GC-analysis using undecane as an internal standard. [d] Yield of isolated product. [e] DMPU was just used as an additive (3.0 equiv. in respect to the organozinc reagent).

Thus, the use of a 1:1 mixture of THF and unpolar solvents such as toluene (entry 4) and *n*-hexane (entry 5) furnished selectively the cross-coupling product (γ,α' -**125a**) in 89% and 82% selectivity, respectively. Switching the solvent to a 1:1 mixture of 1,4-dioxane and THF led to a similar result (81% of γ,α' -**125a**) with an overall yield of 92% (entry 6). Interestingly, significant regioselectivity improvements were achieved by using DMSO, NMP, and DMPU as cosolvents (up to 100% γ,α' -selectivity; entries 7–9), allowing us to isolate the pure coupling product (γ,α' -**125a**) in 91% yield (entry 9 and Scheme 32). Lowering the amount of DMPU to just 3 equivalents led only to a decrease in selectivity (entry 10).

4.3 Tuneable Reactivity in the Allyl-Allyl Cross-Coupling Reaction

Furthermore, by inverting the polarity of the reagents, we were also able to prepare selectively the α,γ' -regioisomer (α,γ' -**125a**). Thus, instead of using prenylzinc bromide (**123a**), we have used directly prenyl bromide (**124b**) and have replaced the allylic bromide (**124a**) with the corresponding zinc reagent (**123b**). Now, the cross-coupling between **124b** and **123b** produced only the regioisomer α,γ' -**125a** with 97% selectivity and 78% yield (Scheme 32).



Scheme 32: Transition-metal-free allyl-allyl cross-coupling leading to the γ,α' -products of type **125** after 3 h at room temperature in very high selectivity (values in parentheses represent the $\gamma,\alpha'/\alpha,\alpha'/\alpha,\gamma'/\gamma,\gamma'$ ratio). [a] LiCl is omitted for clarity. Yield determined by titration with I_2 .

4.4 Preparation of Functionalized 1,5-Dienes

This γ,α' -selectivity was general and the sterically hindered prenylzinc bromide (**123a**) reacts smoothly with the allylic bromides **124c** and **124d** producing the coupling products **125b** and **125c** in 82–91% yield (Table 6, entries 1 and 2).⁸⁴ (*E*)-Non-2-en-1-ylzinc bromide (**123b**) and cinnamylzinc chloride (**123c**) display a similar behavior leading to **125d,e** in 92–96% yield after 3 h (entries 3 and 4). Interestingly, when cinnamylzinc pivalate (**83d**) was used in this cross-coupling the corresponding product was obtained with the same yield (96%; entry 4). In addition, geranylzinc bromide (**123d**) and nerylzinc bromide (**123e**) react with the functionalized allylic bromides **124e** and **124c** furnishing the branched isomers **125f** and **125g** in 90–92% yield (entries 5 and 6). Remarkably, the substituted allylzinc compounds **123f**⁸⁵ and **123g**⁸⁶ react smoothly with the allylic bromide **124f** and prenyl bromide (**124b**) leading to the polyfunctionalized products (**125h,i**) in 83–90% yield (entries 7 and 8). Similarly, the allylic zinc reagents **123a** and **123d** were converted into the corresponding products (γ,α' -**125j** and γ,α' -**125k**) in 79–83% yield (entries 9 and 10). Finally, the allylzinc reagent **123h** reacts twice with (*E*)-1,4-dibromobut-2-ene (**124h**) furnishing the symmetrical product (*E*)-**125l** as the only isomer (*E/Z*>99:1) in 90% yield after 3 h (entry 11).

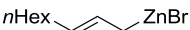

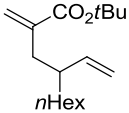
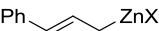

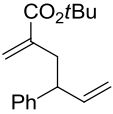
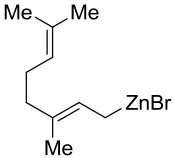

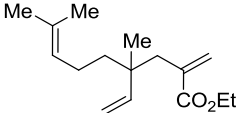
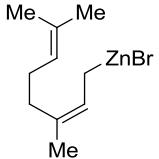

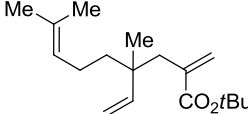
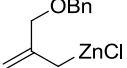
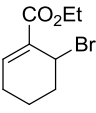
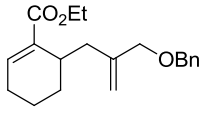
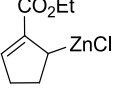
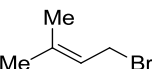
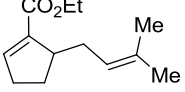
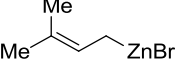
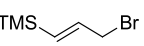
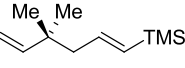
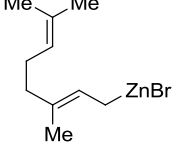
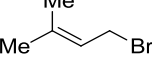
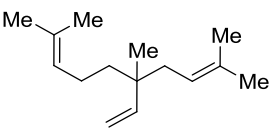
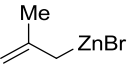
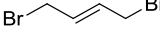
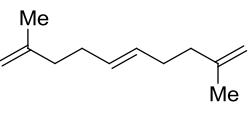
Table 6: Allyl-allyl cross-couplings in a 1:1 mixture of THF and DMPU within 1–3 h at 25 °C

Entry	Zinc Reagent ^[a]	Electrophile ^[b]	Product ^[c]
1	 123a	 124c	 125b : 82%
2	 123a	 124d	 125c : 91%

⁸⁴ The use of allylic chlorides led in several cases to significantly lower yields.

⁸⁵ J. van der Louw, J. L. van der Baan, F. Bickelhaupt, G. W. Klumpp, *Tetrahedron Lett.* **1987**, 28, 2889.

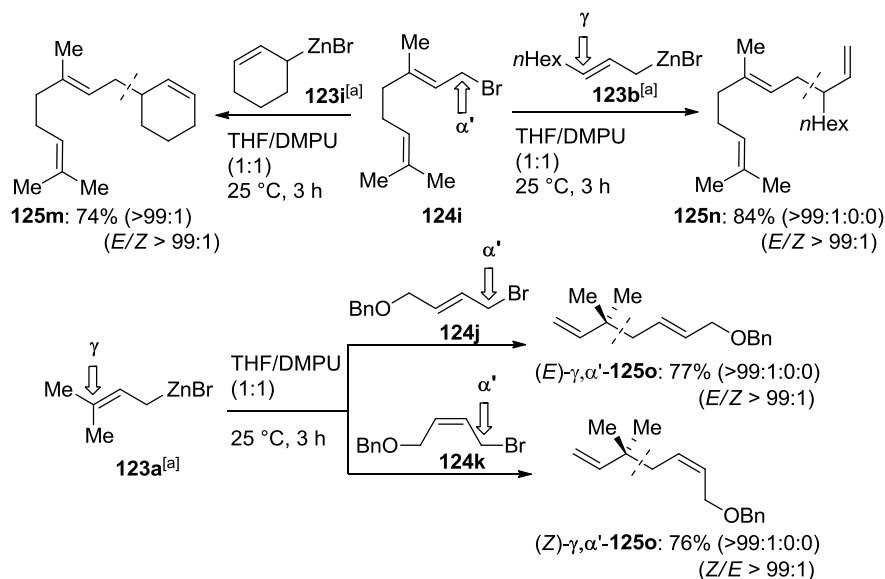
⁸⁶ N. El Alami, C. Belaud, J. Villieras, *J. Organomet. Chem.* **1988**, 348, 1.

3	 123b (25, 2 h, 77)	 124c	 125d : 92%
4	 X = Cl: 123c (25, 2 h, 86) X = OPiv: 83d	 124c	 125e , X = Cl: 96% X = OPiv: 96%
5	 123d (25, 1 h, 83)	 124e	 125f : 92%
6	 123e (25, 1 h, 58)	 124c	 125g : 90%
7	 123f (50, 8 h, 41)	 124f	 125h : 90%
8	 123g (25, 1 h, 60)	 124b	 125i : 83%
9	 123a	 124g	 125j : 79%
10	 123d	 124b	 125k : 83% ^[d]
11	 123h ^[e] (25, 1 h, 66)	 124h	 125l : 90%

[a] LiCl is omitted for clarity. In parentheses: temperature, time, yield [%] for the insertion. Yields determined by titration with I₂. [b] 0.8 equiv. of electrophile were used. [c] Yields refer to analytically pure products. [d] 6% of the α,α'-isomer was formed. [e] 2.4 equiv. of organozinc were used.

4.5 Preparation of Functionalized 1,5-Dienes with Retention of the Double Bond Configuration

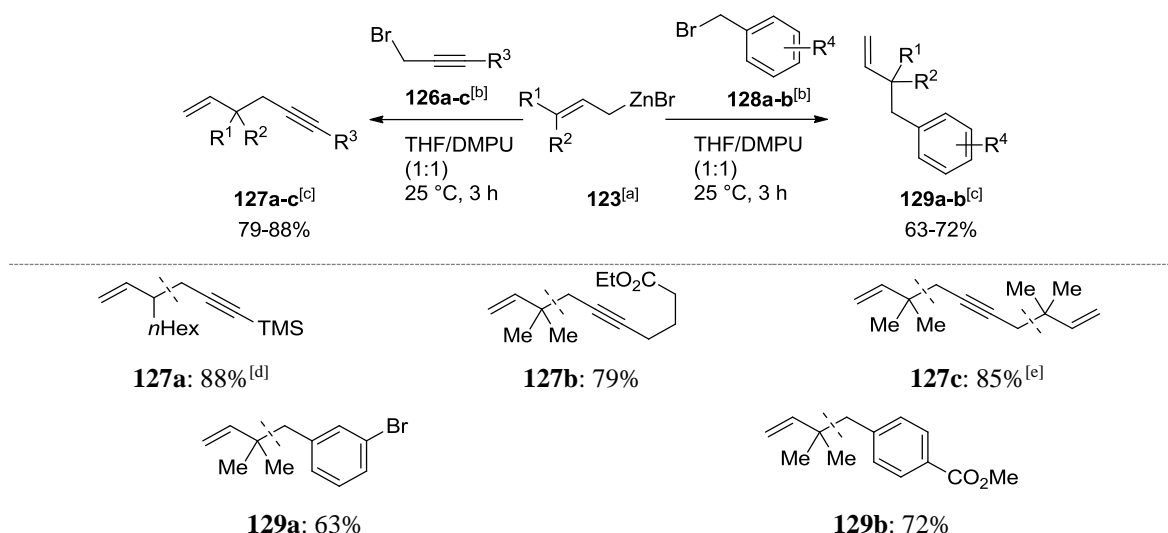
Remarkably, these cross-couplings proceed with retention of the double bond configuration of the allylic bromide indicating an S_N2 -type substitution. Thus, the zinc reagents **123i** and **123b** react with geranyl bromide (**124i**) selectively to give the corresponding (*E*)-1,5,9-trienes (**125m,n**) in 74–84% yield (Scheme 33). In a control experiment, prenylzinc bromide (**123a**) was treated with the (*E*)- and (*Z*)-allylic bromides **124j,k** providing stereoselectively the expected γ,α' -regioisomers (*E*)- γ,α' -**125o** and (*Z*)- γ,α' -**125o** in 76–77% yield and >99% retention of the double bond configuration (Scheme 33).



Scheme 33: Allyl-allyl cross-couplings leading to the γ,α' -products of type **125** with full retention of the double bond configuration. [a] LiCl is omitted for clarity.

4.6 Extension of the Cross-Coupling to Benzylic and Propargylic Halides

This cross-coupling was also applicable to benzylic and propargylic halides. Thus, the reaction of prenylzinc bromide (**123a**) and (*E*)-non-2-en-1-ylzinc bromide (**123b**) with propargylic halides of type **126** produces 1,5-enynes of type **127** (Scheme 34). Accordingly, the cross-coupling of **123b** with the propargylic chloride **126a** provides only the 1,5-enyne **127a** in 88% yield.



Scheme 34: Cross-coupling of allylic zinc reagents of type **123** with propargylic and benzylic halides leading to the γ,α' -products of type **127** and **129**. [a] LiCl is omitted for clarity. [b] 0.80 equiv. of electrophile were used. [c] Yields refer to analytically pure products. [d] The propargylic chloride was used instead of the bromide. [e] 0.40 equiv. of electrophile were used.

The reaction of prenylzinc bromide (**123a**) with ethyl 7-bromohept-5-ynoate (**126b**) furnishes the corresponding functionalized 1,5-enyne **127b** in 79% yield. Furthermore, the coupling of zinc reagent **123a** with 1,4-dibromobut-2-yne (**126c**) selectively affords the symmetrical product **127c** in 85% yield. Interestingly, benzyl bromides (**128a,b**) reacted under our standard reaction conditions furnishing the substitution products **129a** and **129b** in 63–72% yield. However, prenylzinc bromide did not react with 1-bromononane. In addition, in a control experiment, prenylzinc bromide (**123a**) was added to a 1:1 mixture of 1-bromononane and (*E*)-1-bromonon-2-ene (**124a**) which led to the allyl–allyl cross-coupling product γ,α' -**125a** exclusively.

4.7 Theoretical Investigations on the Reaction Mechanism

In order to support the experimental outcome of this selective transformation the reaction pathway was investigated using double hybrid density functional theory (DFT).^{87,88} The addition of LiCl is currently believed to accelerate reactions of organometallic reagents through increased formation of monomeric species or ate-like complexes.⁸⁹ In line with this rationalization we find that hetero dimers of type **130**

⁸⁷ These calculations were performed by Florian Achrainer and are given here for the sake of completeness.

⁸⁸ Geometries of the corresponding organozinc intermediates have been obtained at B3LYP/631SVP level, followed by single-point calculations at B2PLYP-D3(FC)/def2-TZVPP level. Solvent effects have been included using Truhlar's solvent model density (SMD) in combination with B3LYP/6-31G(d) calculations and THF or DMF as respective solvents.

⁸⁹ a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, 28, 771; b) G. T. Achonduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2010**, 46, 4109; c) E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2011**, 50, 6448; d) B. Lecachey, H. Oulyadi, P. Lameiras, A. Harrison-Marchand, H. Gérard, J. Maddaluno, *J. Org. Chem.* **2010**, 75, 5976; e) D. Stern, N. Finkelmeier, D. Stalke, *Chem. Comm.* **2011**, 47, 2113; f) A. C. Hoepker, L. Gupta, M. F. Faggini, D. B. Collum, *J. Am. Chem. Soc.* **2011**, 133, 7135; g) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, 30, 5018.

represent the most stable structures in solution; this is indicated by the significant exergonicity of the exchange reaction of $(\text{LiCl})_2(\text{sol})_4$ with $(\text{RZnBr})_2(\text{sol})_2$ ($\Delta G_{\text{sol}}(\text{THF}) = -14.4 \text{ kJ mol}^{-1}$, $\Delta G_{\text{sol}}(\text{DMPU}) = -27.1 \text{ kJ mol}^{-1}$) at the B2PLYP-D3(FC)/def2-TZVPP level⁹⁰ including implicit SMD/B3LYP/6-31G(d) solvation.⁹¹ Indeed, ^1H and ^{13}C NMR shifts in THF obtained during the LiCl-mediated oxidative addition of zinc to the carbon–bromine bond of prenyl bromide (**124b**) correlate quite well with theoretically calculated chemical shifts of lithium zinc dimer **130-THF** at the mPW1K/IGLO-III level of theory⁹² (see the Supporting Information). Substituted allylic organometallics often show high diastereoselectivity in reactions with electrophiles due to their rather ordered cyclic or acyclic transition states.⁹³ How LiCl facilitates the construction of highly ordered but unstrained transition states in substitution reactions with prenyl zinc nucleophiles is shown in an exemplary fashion in Figure 4 for the formation of γ,α' -cross-coupling products of type **125**. Starting from mixed aggregate **130-THF**, the reaction is here assumed to involve initial exchange of THF by DMPU. Due to the better donor ability of DMPU, as quantified by the Gutmann donor numbers,⁹⁴ this ligand exchange is exergonic by $\Delta G_{\text{exch}} = -40.9 \text{ kJ mol}^{-1}$. Subsequent exchange of one of the DMPU ligands by the substrate leads to reactant complex **PRC-I** and is endergonic by $\Delta G_{298} = 26.0 \text{ kJ mol}^{-1}$. In the absence of LiCl this step is significantly more costly, and formation of product complex **PRC-II** is endergonic by $\Delta G_{298} = 54.5 \text{ kJ mol}^{-1}$. Subsequent reaction barriers are much lower for LiCl-containing transition state **TS-I** as compared to its LiCl-free analogue **TS-II**, the difference amounting to $\Delta\Delta G^\ddagger (\text{TS-I/TS-II}) = 48.7 \text{ kJ mol}^{-1}$.⁹⁵

⁹⁰ a) L. Goerigk, S. Grimme, *J. Chem. Theory Comput.* **2011**, 7, 291; b) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, 7, 3297; c) F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, 8, 1057.

⁹¹ A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, 113, 6378. ΔG_{sol} (THF) includes implicit solvation in THF, ΔG_{sol} (DMPU) in a DMF continuum.

⁹² P. Quinio, C. François, A. E. Escibano Cuesta, A. K. Steib, F. Achraimer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, 17, 1010.

⁹³ M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, 113, 5595.

⁹⁴ DN (THF) = 20 kcal mol⁻¹, DN (NMP) = 27.3 kcal mol⁻¹, DN (*N,N*-dimethylacetamide) = 27.8 kcal mol⁻¹ taken from V. Gutmann, *Coord. Chem. Rev.* **1976**, 18, 225.

⁹⁵ The selectivity increase observed by the use of non-polar solvents (entries 4 and 5 of Table 1) can be tentatively explained by the higher Lewis-acidity of the zinc cation in these solvents favoring the **TS-I**.

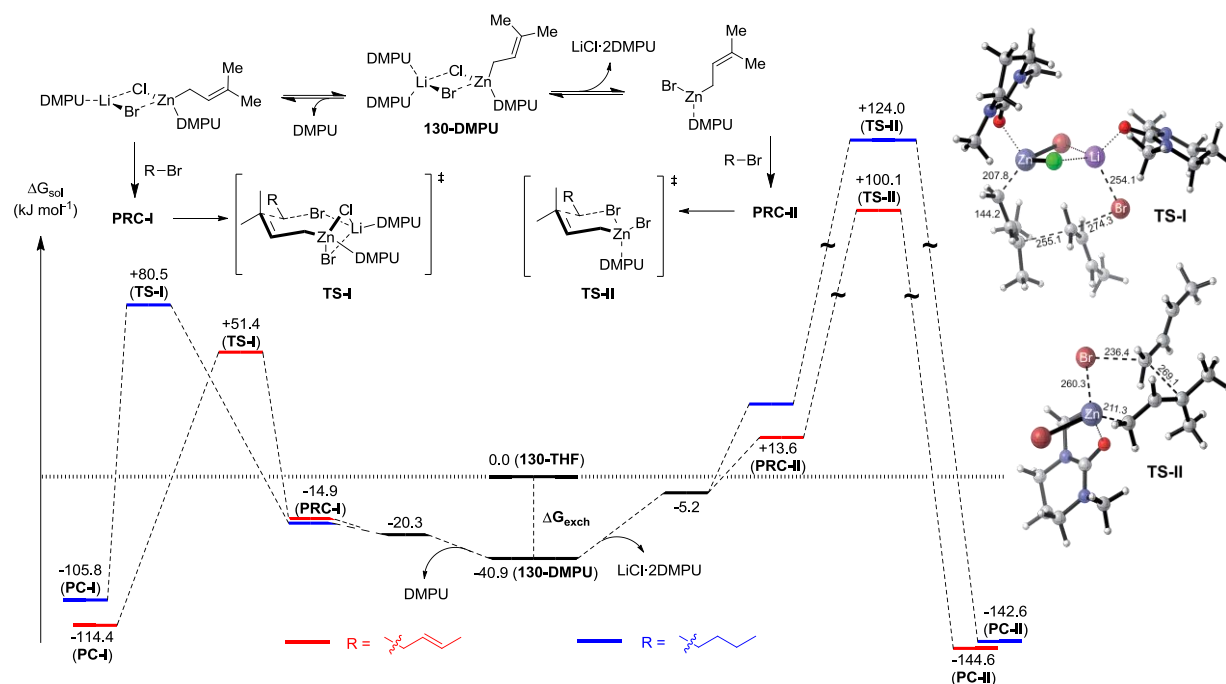


Figure 4: Reaction pathway of the γ,α' -cross-coupling in THF solution (B2PLYP-D3(FC)/def2-TZVPP + ΔG_{sol} (SMD/B3LYP/6-31G(d)), in kJ mol⁻¹) and graphical representation of the B3LYP/631SVP optimized transition states **TS-I** and **TS-II** (bond lengths in pm).⁹⁶

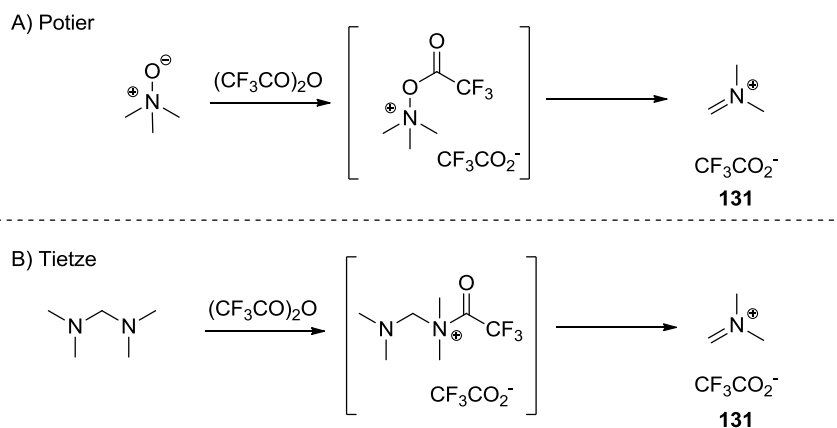
The main structural difference between these transition states concerns the trajectory angle of the backside attack: while the ideal angle of 180° is nearly reached in **TS-I** with a value of 163°, compared to **TS-II** with 134°. This indicates that geometrical factors as well as electronic interactions play an important role in decreasing the kinetic barrier. Replacement of the allylic bromide by *n*-butyl bromide leads to barriers significantly higher in energy ($\Delta\Delta G^\ddagger(\text{TS-I}) = 29.1 \text{ kJ mol}^{-1}$, $\Delta\Delta G^\ddagger(\text{TS-II}) = 23.9 \text{ kJ mol}^{-1}$), which is in agreement with the competition experiment of 1-bromononane and (*E*)-1-bromonon-2-ene (**124a**). This behavior can be rationalized by inspection of the HOMO and LUMO levels which shows a larger energy difference for the respective aliphatic bromide and an increased substrate deformation energy in the respective transition state.^[25] In conclusion, the presence of LiCl seems essential for fast and selective cross-couplings. In fact, complex mixtures of products are obtained in the absence of LiCl.

⁹⁶ These calculations were performed by Florian Achraimer and are given here for the sake of completeness.

5 Preparation of Tertiary Amines by the Reaction of Iminium Ions Derived from Unsymmetrical Aminals with Zinc and Magnesium Organometallics

5.1 Introduction

The preparation of functionalized unsaturated amines is an important task in organic chemistry since many polyfunctional amino compounds are of interest due to their biological activity. A wide range of preparation methods have been reported,⁹⁷ including the reaction of organometallic compounds with iminium ions.⁹⁸ One suitable electrophile is the salt *N,N*-dimethyl(methylene)iminium trifluoroacetate (**131**) which was first prepared by Potier from trimethylamine oxide (Scheme 35, A).⁹⁹ An improved synthesis was reported by Tietze, who used *N,N,N',N'*-tetramethylmethanediamine (TMDAM) and trifluoroacetic anhydride (TFAA) (Scheme 35, B).¹⁰⁰



Scheme 35: Preparation of *N,N*-dimethyl(methylene)iminium trifluoroacetate (**131**) starting from trimethylamine oxide (A) or from the symmetrical aminal *N,N,N',N'*-tetramethylmethanediamine (TMDAM) (B).

Thus, Knochel et al. reported the reaction of aromatic, benzylic and alkyl-magnesium and -zinc reagents with iminium ions derived from symmetric aminals and $(\text{CF}_3\text{CO})_2\text{O}$ according to Tietze's protocol (Scheme 36, A).¹⁰¹ Furthermore, it was shown that polyfunctional unsaturated amines can be prepared by the reaction of unsaturated iminium ions with Grignard reagents (Scheme 36, B).¹⁰²

⁹⁷ For selected reviews, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, 99, 1069; b) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, 574, 125; c) B. List, *Tetrahedron* **2002**, 58, 5573; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. MacMillan, *J. Am. Chem. Soc.* **2006**, 128, 84; e) M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166; f) J. L. Klinkenberg, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, 50, 86; g) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, 111, 1780.

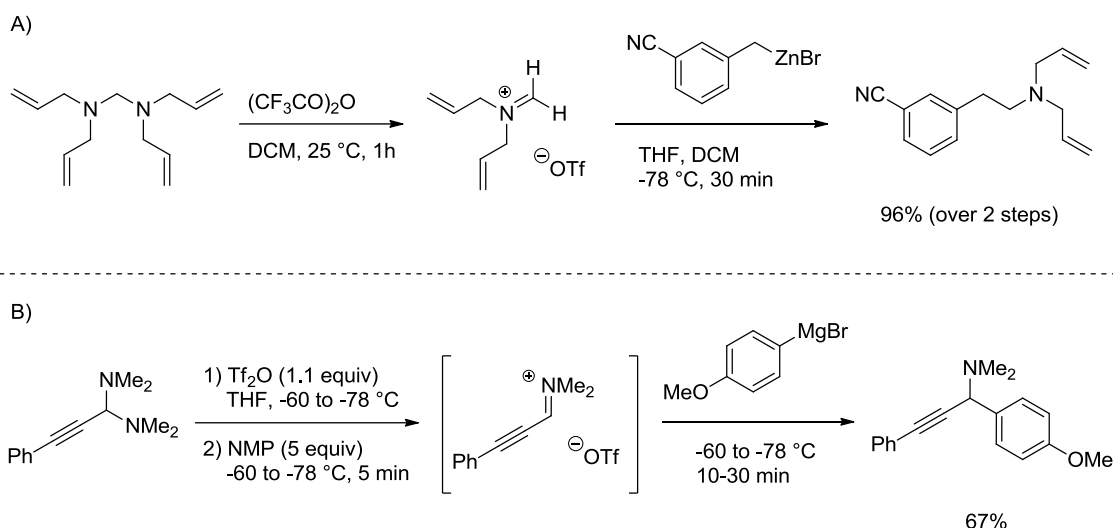
⁹⁸ a) N. L. Holy, *Synth. Commun.* **1976**, 6, 539; b) N. L. Holy, Y. F. Wang, *J. Am. Chem. Soc.* **1977**, 99, 944; c) J. L. Roberts, S. Borromeo, C. D. Poulter, *Tetrahedron Lett.* **1977**, 15, 1299; d) N. Holy, R. Fowler, E. Burnett, R. Lorenz, *Tetrahedron* **1979**, 35, 613; e) T. A. Bryson, G. H. Bonitz, C. J. Reichel, R. E. Dardis, *J. Org. Chem.* **1980**, 45, 534.

⁹⁹ A. Ahound, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, P. Potier, *J. Am. Chem. Soc.* **1968**, 90, 5622.

¹⁰⁰ G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, 15, 239.

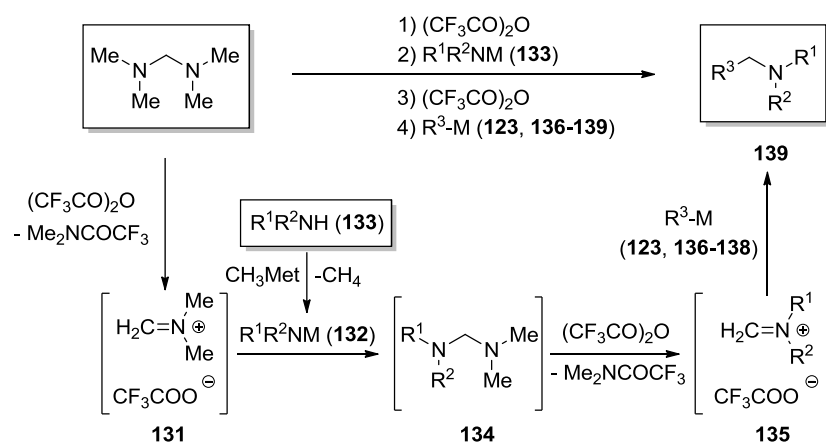
¹⁰¹ N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, 941.

¹⁰² N. Gommermann, C. Konradin, P. Knochel, *Synthesis* **2002**, 2143.



Scheme 36: A) Preparation of tertiary amines by the reaction of organozinc reagents with iminium ions;¹⁰¹ B) Addition of functionalized organomagnesium reagents to unsaturated iminium ions.¹⁰²

As a logical consequence, we envisioned the preparation of new unsymmetrical aminals by the reaction of **131** with metallic amides **132** (R^1R^2NMe ; $M = Li, MgX$). The amides **132** were prepared by deprotonation of the corresponding amine R^1R^2NH (**133**) with CH_3Met ($M = Li, MgX$). The addition of TFAA to the aminals of type **134** will provide a route to complex iminium ions of type **135**. It is expected that the acylation of aminals with TFAA occurs selectively on the least sterically hindered side of the aminal. The resulting iminium salt **135** could show a similar behavior and lead after reaction with organometallics of type **123** and **136–138** (R^3-Met) to polyfunctional tertiary amines of type **139** (Scheme 37).

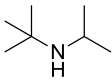
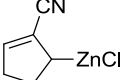
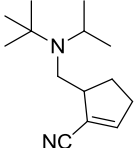
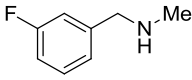
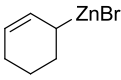
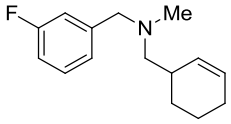
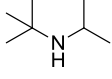
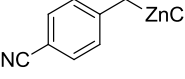
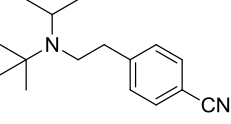


Scheme 37: Preparation of tertiary amines by cleavage of mixed aminals **134** to mixed iminium ions **135** and subsequent reaction with organometallic reagents.

5.2 One-Pot Procedure for the Reaction of Organometallic Reagents with Unsymmetrical Iminium Ions

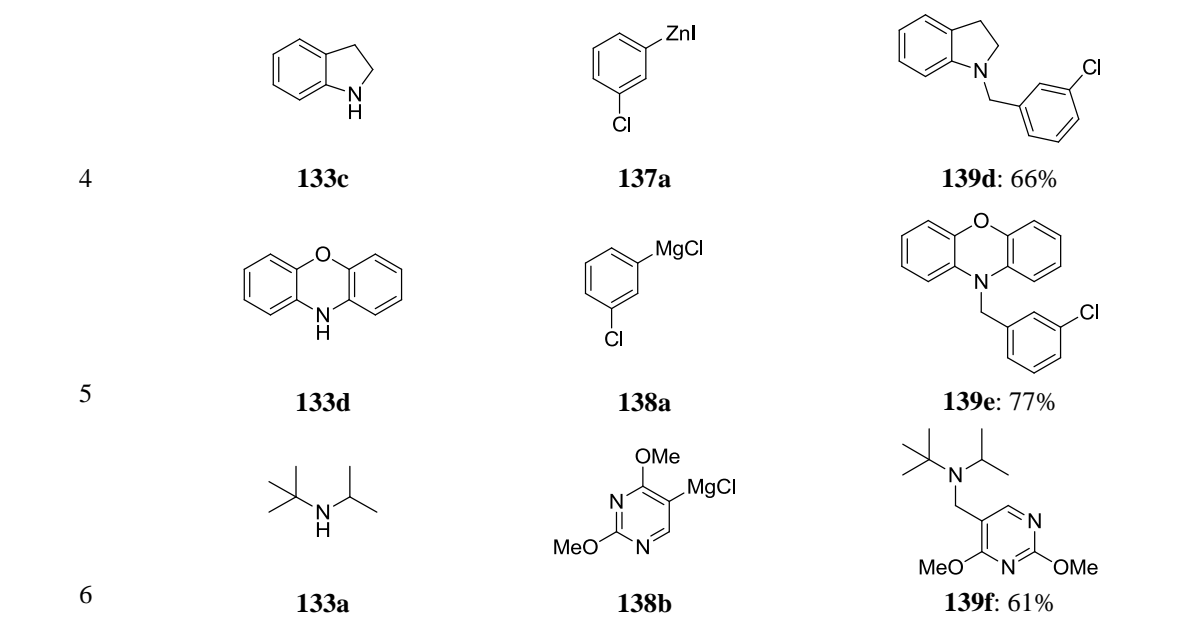
This one-pot procedure proved to be general and a range of functionalized amines of type **133** as well as a variety of organometallic reagents (**123** and **136–138**) were used, leading to various tertiary amines (**139a–f**) in 61–84% overall yield (Table 7, entries 1–6). Thus, the allylic reagents **123g,i** furnished the functionalized homoallylic amines **139a,b** in 76–84% yield. The sterically hindered amine **133a** furthermore reacted with benzylzinc reagent **136a** furnishing phenethylamine **139c** in 72% yield. In addition, this reaction was successfully performed on gram-scale (72% yield on a 1 mmol scale compared to 68% yield on a 10 mmol scale). Phenethylamines are common targets in medicinal chemistry and have found many applications in neuropsychopharmacology.¹⁰³ Other classes of zinc reagents¹⁰⁴ were successfully used in this homologative synthesis of tertiary amines. Thus, the aminomethylation of the arylzinc iodide (**137a**) with indoline (**133c**) provided the benzylamine **139d** in 66% yield. Furthermore, aryl and heteroaryl Grignard reagents **138a,b** were used in this one-pot homologative amination, furnishing highly functionalized benzylamines. Thus, phenoxazine (**133d**) and *N*-*tert*-butylisopropylamine (**133a**) were converted to the corresponding benzylamines **139e** and **139f** in 61–77% yield, using the Grignard reagents **138a** and **138b**.

Table 7: Tertiary amines of type **139** obtained by the one-pot reaction of amines of type **133** with various organometallic reagents

Entry	Amine	Zinc Reagent ^[a]	Product ^{[b],[c]}
1	 133a	 123g	 139a : 84%
2	 133b	 123i	 139b : 76%
3	 133a	 136a	 139c : 72% (68%) ^[d]

¹⁰³ a) G. K. Aghajanian, G. J. Marek, *Brain Res. Rev.* **2000**, *31*, 302; b) S. L. Hill, S. H. L. Thomas, *Clin. Toxicol.* **2011**, *49*, 705.

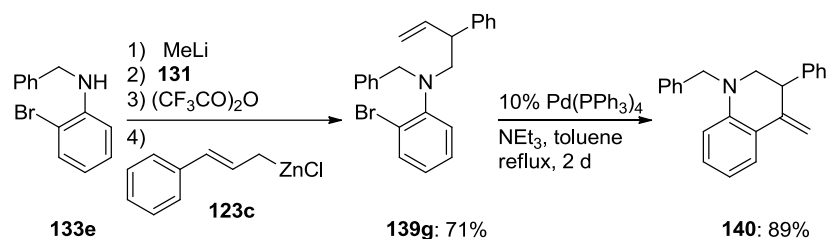
¹⁰⁴ a) *Organozinc Reagents*; P. Knochel, P. Jones, Eds.; Oxford University Press: New York, **1999**; b) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, *58*, 417; c) B. Haag, M. Mosrin, I. Hiriyakkanavar, V. Malakhov, P. Knochel, *Angew. Chem.* **2011**, *123*, 9968; *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.



[a] The concentration of the zinc reagent was determined by iodometric titration. [b] Isolated yield of analytically pure product. [c] The reaction was performed on a 1 mmol scale. [d] The reaction was performed on a 10 mmol scale.

5.3 Preparation of Functionalized Precursors Suitable for Cyclization Reactions

The high functional group tolerance of this procedure enabled the synthesis of functionalized precursors suitable for cyclization reactions. This was demonstrated in the homologation of the amine **133e**, which led to an intermediate iminium ion that reacted *regioselectively* with cinnamylzinc chloride (**123c**) to the polyfunctional aniline **139g** in 71% yield. A subsequent Heck cyclization^[19] led selectively to the *exo*-methylene quinolidine (**140**) in 89% yield.

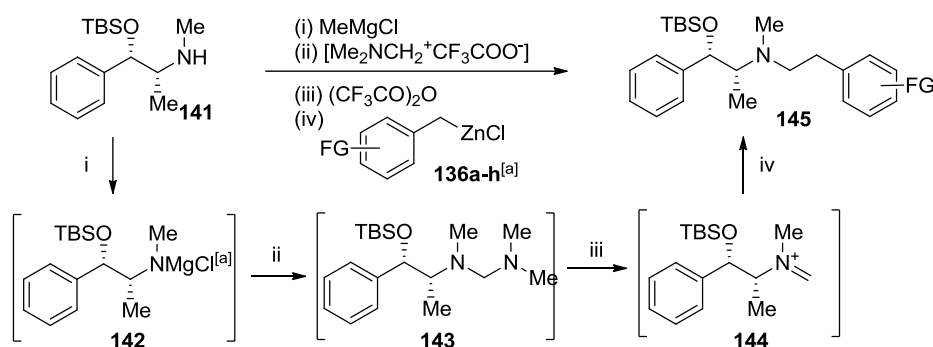


Scheme 38: Heck reaction of the aniline derivative **139g**, which was obtained by the one-pot reaction of aniline (**133e**) and cinnamylzinc chloride (**123c**).

5.3.1 Synthesis of Novel Ephedrine Derivatives Containing a Tertiary Amine

As shown in Chapter 5.2, this one-pot procedure proved to be general for the use of a range of functionalized amines as well as a variety of benzylic zinc reagents, leading selectively to the corresponding phenethylamines. The homologative amination procedure furthermore allowed the conversion of ephedrine derivatives to the corresponding benzylic and phenethyl amines which showed a promising structure for biological evaluation. Thus, the treatment of a THF solution of TBS protected (+)-ephedrine derivative (+)-**141** with MeMgCl (1.1 equiv. 2.8 M in THF, $-20\text{ }^{\circ}\text{C}$, 30 min)

provided the corresponding magnesium amide, which was added to the *Potier* salt $[\text{Me}_2\text{NCH}_2^+\text{CF}_3\text{COO}^-]$ (**131**), generated by the addition of trifluoroacetic anhydride (TFAA) (1.0 equiv.) to TMDAM (1.0 equiv., CH_2Cl_2 , -20°C , 15 min) (Scheme 39). The addition of TFAA (1.0 equiv.) to the aminal thus formed (**143**) led after 15 min at -20°C selectively to the iminium salt **144** which was then treated with a variety of benzylic zinc reagents of type **136** furnishing the expected tertiary amines of type **145** in 70–91% yield (Scheme 39 and Table 8).

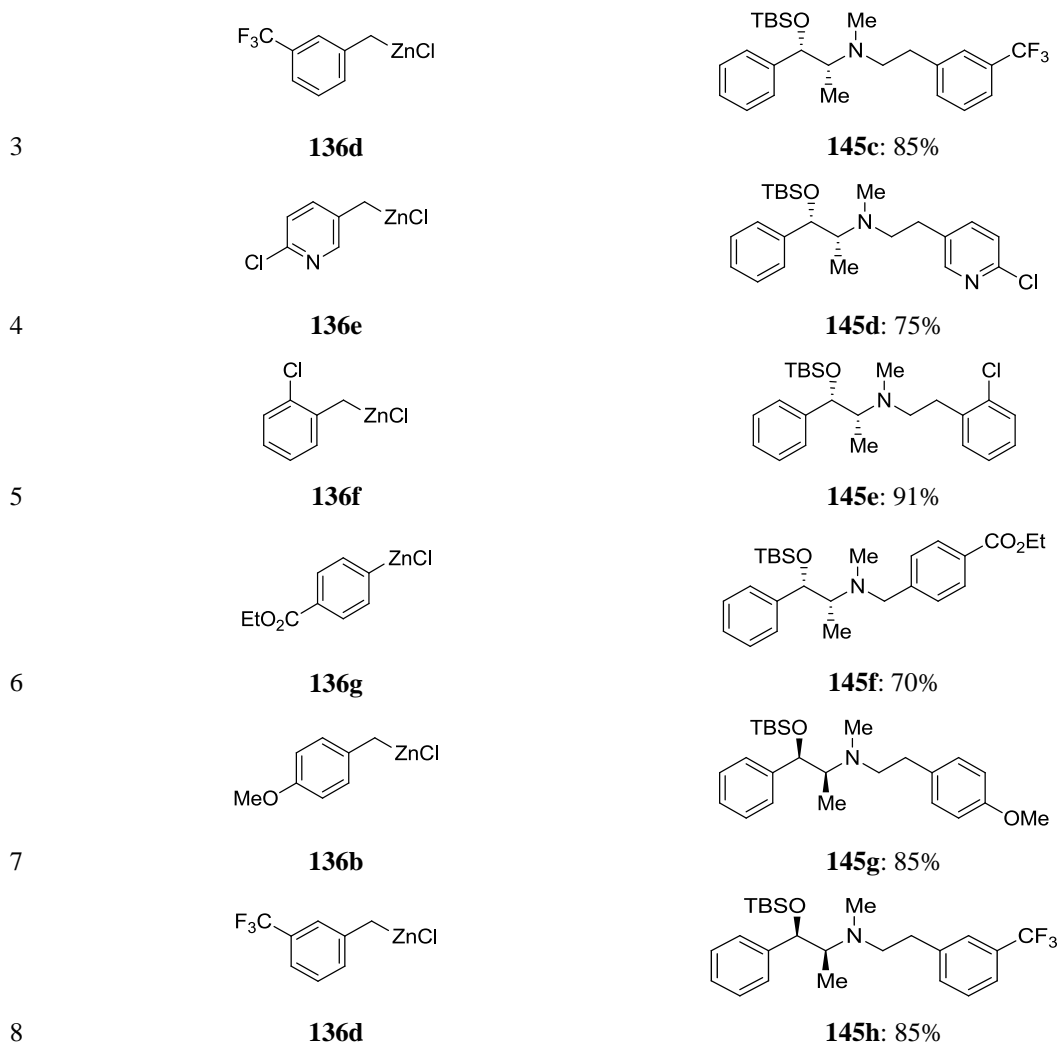


Scheme 39: Preparation of ephedrine derivatives of type **145** containing a tertiary amine by cleavage of the mixed aminal **143** and subsequent reaction with benzylic zinc reagents of type **136**. Conditions: i) MeMgCl (1.1 equiv.), -20°C , 30 min; ii) $[\text{Me}_2\text{NCH}_2^+\text{CF}_3\text{COO}^-]$ (**131**; 1.0 equiv.), -20°C , 30 min; iii) $(\text{CF}_3\text{CO})_2\text{O}$ (1.0 equiv.), -20°C , 15 min; iv) benzylic zinc halide (**136**; 1.1 equiv.), -78°C to room temperature, overnight. [a] LiCl is omitted for clarity.

Thus, (4-methoxybenzyl)zinc chloride (**136b**) and the ester and trifluoromethyl containing benzylic zinc reagents **136c** and **136d** reacted with the iminium ion **144** to form the phenethylamines **145a-c** in 81–85% yield (Table 8, entries 1–3). Interestingly, the heterocyclic and the *ortho*-substituted zinc reagents **136e,f** showed a similar behavior and led selectively to the desired phenethylamines **145d,e** in 75% and 91% yield (entries 4–5). Furthermore, the aromatic zinc reagent **136g** was used according to the same protocol and furnished the benzylic amine **145f** in 70% yield (entry 6). In addition, the (–)-ephedrine derivatives **145g,h** were prepared from the corresponding secondary (–)-ephedrine derivative using (4-methoxybenzyl)zinc chloride (**136b**) and (3-(trifluoromethyl)benzyl)zinc chloride (**136d**) (entries 7–8).

Table 8: Preparation of (+/–)-ephedrine derivatives of type **145** in a one pot procedure

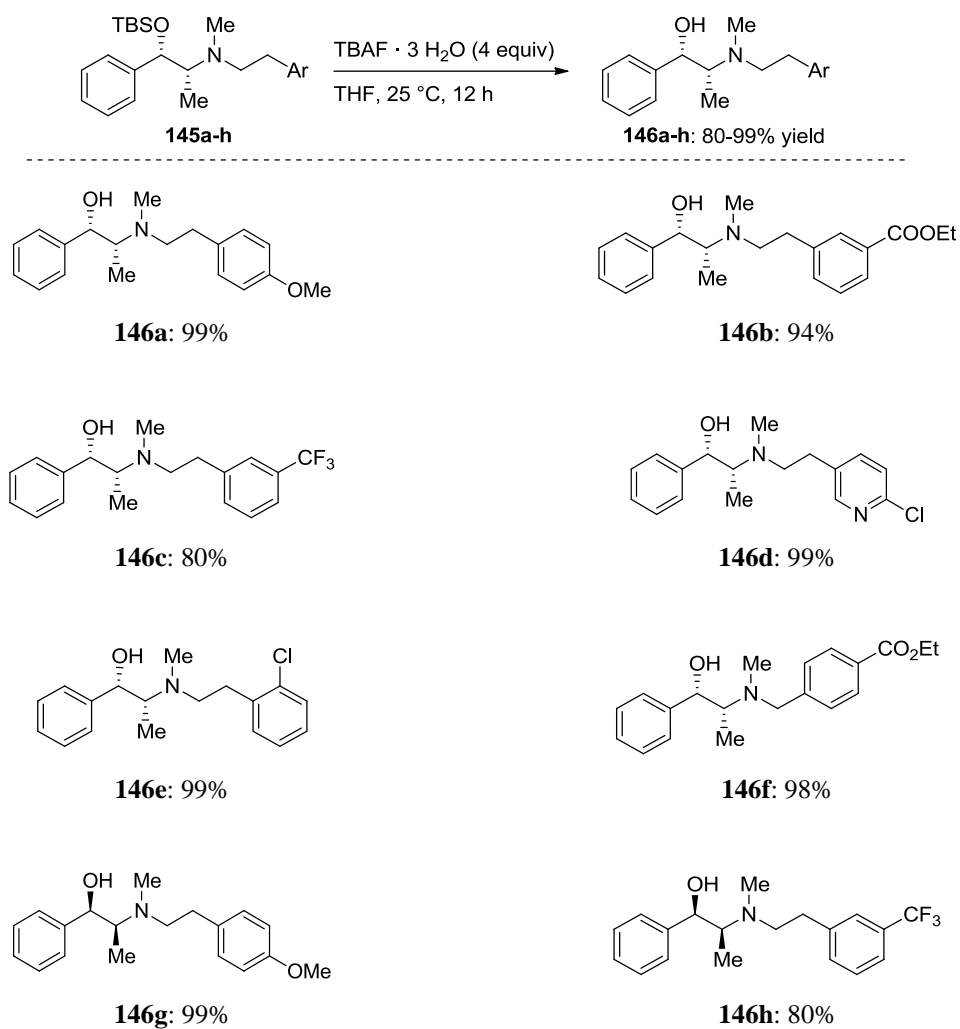
Entry	Zinc Reagent ^[a]	Product ^[b]
1	 136b	 145a : 85%
2	 136c	 145b : 81%



[a] Complexed LiCl is omitted for clarity. [b] Yields refer to analytically pure products.

5.3.2 Deprotection of the Alcohol Using TBAF

The facile and smooth removal of the TBS group was shown by the conversion of several TBS protected phenethylamines of type **145** to the corresponding alcohols using TBAF·3H₂O (4 equiv., THF, 25 °C, 12 h). Thus, the ephedrine derivatives **146a-h** were obtained in 80–99% yield (Scheme 40).



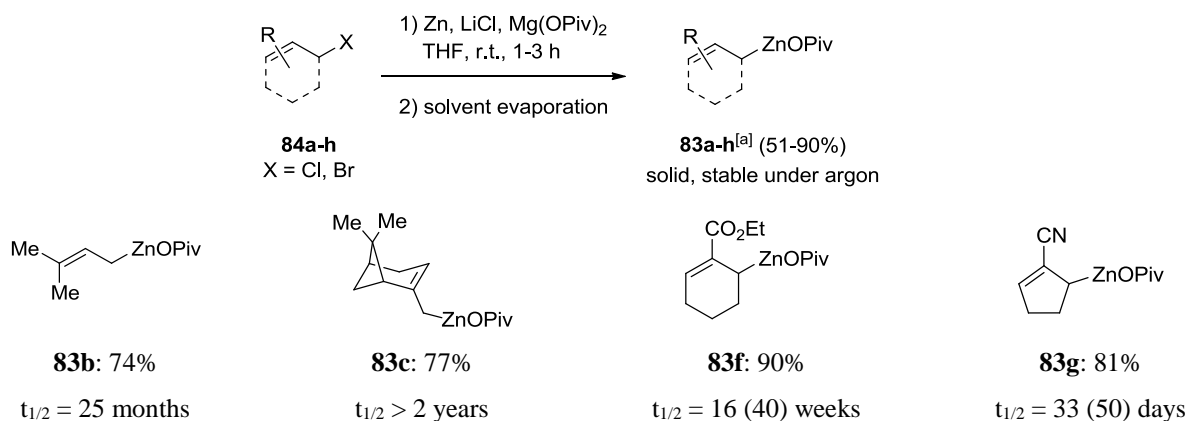
Scheme 40: TBS deprotection of tertiary amines **145a-h** to the corresponding alcohols **146a-h** which could be subjected to biological evaluation.

6 Summary

This work focused on the development of solid allylzinc reagents prepared from the corresponding allylic bromides or chlorides through a one-pot insertion under mild conditions with commercial zinc powder, LiCl, and Mg(OPiv)₂. After evaporation of the solvent, the resulting solid allylic zinc reagents can be stored under argon for an extended period of time ($t_{1/2}$ between ca. 5 weeks and >2 years). These reagents show excellent reactivity in Pd-catalyzed cross-coupling reactions with aryl bromides when using PEPPSI-IPent and they undergo smooth additions to methyl ketones and aldehydes with high diastereoselectivity. In addition, the regioselective acylation of the reagents with acid chlorides produces β,γ -unsaturated ketones. Furthermore, the lack of air-stable organozinc enolates was overcome by a mild and convenient preparation of solid, salt stabilized zinc amide enolates which show an exceptional stability when exposed to air and furthermore react with a large variety of electrophiles. Moreover, the scalable preparation of (hetero-)aromatic zinc pivalates was established as a valuable tool for both synthetic and medicinal chemists for instance in high throughput screenings. In addition, it was demonstrated that allylic zinc reagents undergo highly regioselective cross-couplings with allylic bromides via an S_N2-substitution fashion in a 1:1 mixture of THF and DMPU. Furthermore, unsymmetrical allylic zinc reagents undergo this cross-coupling almost exclusively from the most branched side of the allylic system. The stereochemistry of the double bond of the allylic bromide is maintained during the cross-coupling. This S_N2-reaction can be extended to propargylic and benzylic bromides. Finally, a general synthesis of new mixed aminals using Tietze's iminium salt was developed. The treatment of these aminals with TFAA provided an entry to new polyfunctional iminium salts, which were trapped by numerous zinc and magnesium organometallics leading to a range of valuable amines using a convenient one-pot procedure. This reaction sequence allowed the preparation of complex amines, including biorelevant phenethylamines and ephedrine derivatives as well as a cyclization precursor, leading to the quinolidine scaffold.

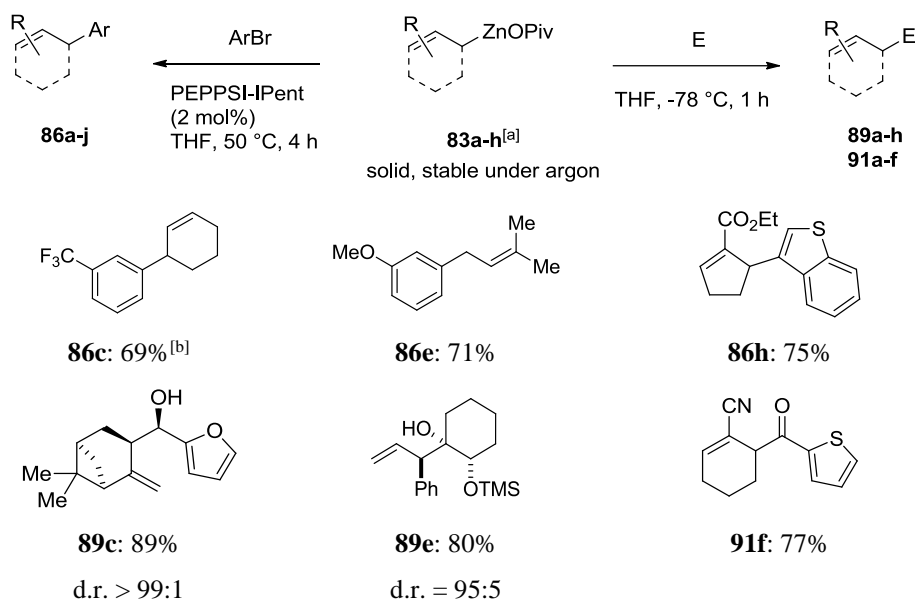
6.1 Preparation of Solid, Substituted Allylic Zinc Reagents and Their Reactions with Electrophiles

The treatment of various allylic chlorides or bromides with zinc dust in the presence of lithium chloride and magnesium pivalate (Mg(OCOtBu)₂) in THF affords allylic zinc reagents which, after evaporation of the solvent, produce solid zinc reagents that display excellent thermal stability (Scheme 41).



Scheme 41: Preparation of solid functionalized allylzinc pivalates of type **83** from the corresponding allylic halides of type **84** by using Zn, Mg(OPiv)₂ and LiCl. Values given in brackets show the half-lives when the reagents were stored at $-24\text{ }^{\circ}\text{C}$. [a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity.

The reactivity of the novel allylic zinc pivalates in Pd-catalyzed cross-couplings with various unsaturated bromides in the presence of various Pd-catalysts was examined. In our hands, PEPPSI-IPent gave by far the best results. In addition, the solid allylic zinc reagents of type **83** react as previously reported allylic zinc halides with electrophiles such as carbonyl derivatives or acid chlorides with complete regioselectivity (formation of the new carbon-carbon bond from the most substituted end of the allylic system) and very high diastereoselectivity as shown in Scheme 42.

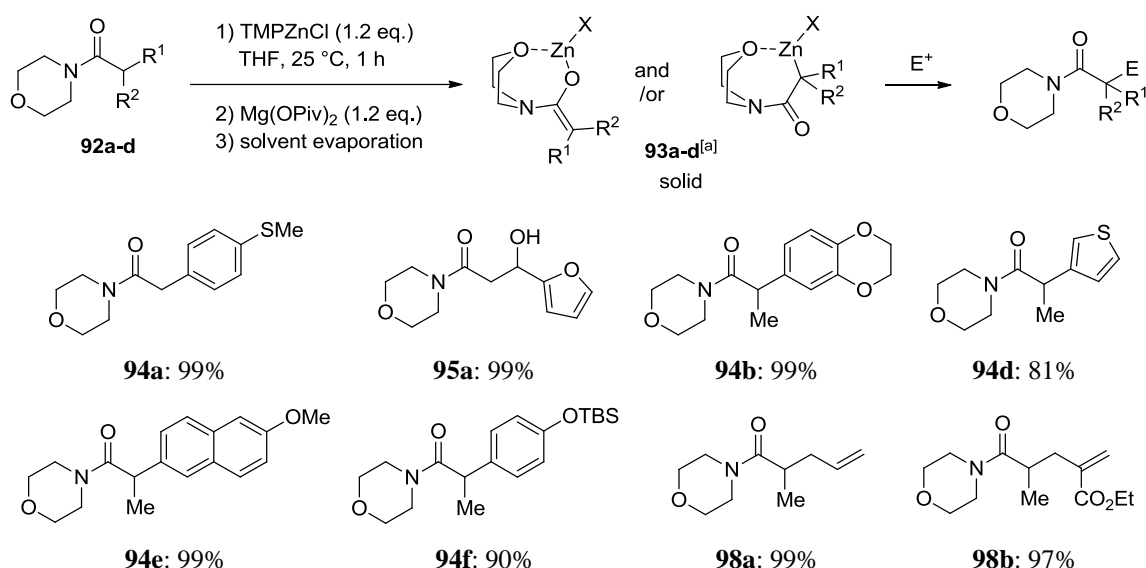


Scheme 42: PEPPSI-IPent-catalyzed cross-coupling and reaction with various electrophiles of allylic organozinc pivalates of type **83** in THF.

6.2 Preparation and Application of Solid, Salt Stabilized Amide Enolates

A first general approach toward the preparation of solid, salt stabilized organozinc enolates *via* deprotonation using various metal TMP bases was developed. Thus, different morpholineamide zinc

pivalates were prepared from the corresponding morpholine amides under mild conditions and are obtained as easy-to-handle solids after evaporation of the solvent. These reagents show an excellent stability upon air-exposure and are furthermore suitable for a long-term storage under argon. In addition, these reagents undergo smooth Negishi cross-couplings with aryl bromides and iodides and furthermore react with carbonyl compounds to form the corresponding alcohols (Scheme 43). Moreover copper catalyzed allylation reactions were performed efficiently.

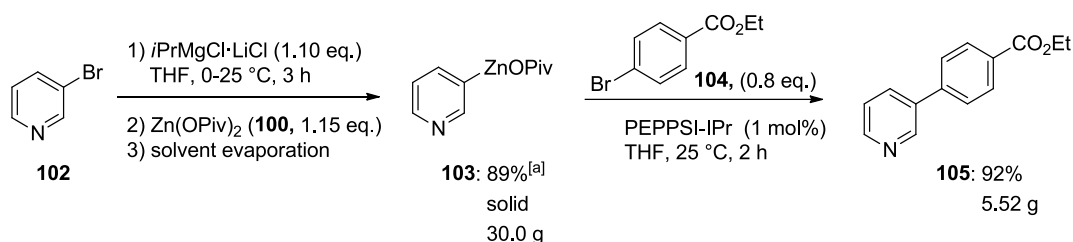


Scheme 43: Preparation of solid zinc amide enolates of type **93** from the corresponding morphonyl amides of type **92** by using TMPZnCl·LiCl (**19**) in the presence of Mg(OPiv)₂ and subsequent reactions with various electrophiles. [a] Complexed Mg(OPiv)Cl and LiCl are omitted for clarity.

6.3 Scalable Preparation of Functionalized (Hetero-)Arylzinc Pivalates

The limited stability towards air and moisture represents a serious drawback of aromatic and heterocyclic organozinc reagents for their practical use in the laboratory and for industrial applications. To overcome this problem, we recently developed a method for the preparation of aryl and heteroaryl zinc pivalates, which are easy-to-handle solids with exceptional stability when exposed to air. To evaluate their use in industry applications e.g., in high throughput screenings in medicinal chemistry a

scale up procedure was developed for the preparation of solid pyridin-3-ylzinc pivalate (**103**) and the subsequent Pd-catalyzed cross-coupling to ethyl 4-(pyridin-3-yl)benzoate (**105**) (Scheme 44).



Scheme 44: Scalable protocol for the preparation of pyridin-3-ylzinc pivalate (**103**) cross-coupling to ethyl 4-(pyridin-3-yl)benzoate (**105**). [a] Complexed $\text{Mg}(\text{OPiv})\text{Br}$ and LiCl are omitted for clarity.

With this optimized preparation protocol in hands, various polyfunctional benzylic, aryl- and heteroarylzinc pivalates **106–122** were prepared on a 7.0 mmol scale each and stored in sealed/inerted ampules containing approximately 0.125 mmol of each reagent (Figure 5). This set of reagents could be used for high throughput screenings in medicinal chemistry e.g., in a late stage functionalization of drugs *via* palladium catalyzed Negishi cross-couplings.

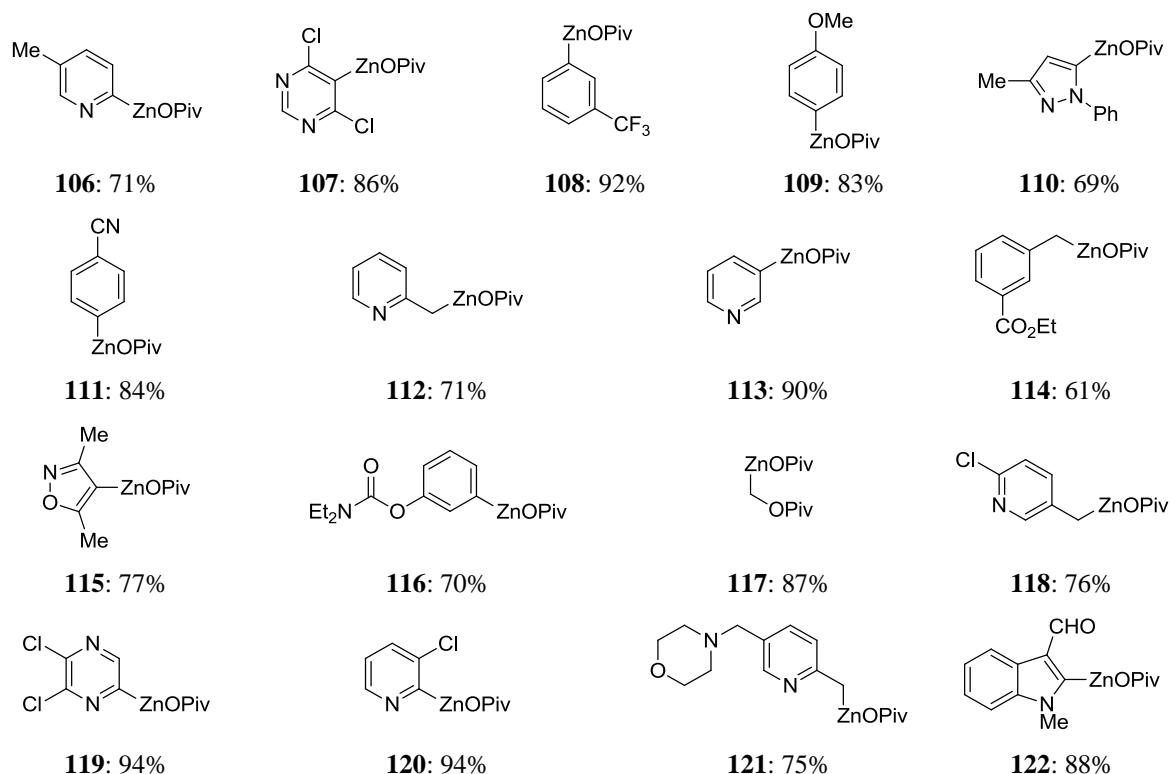
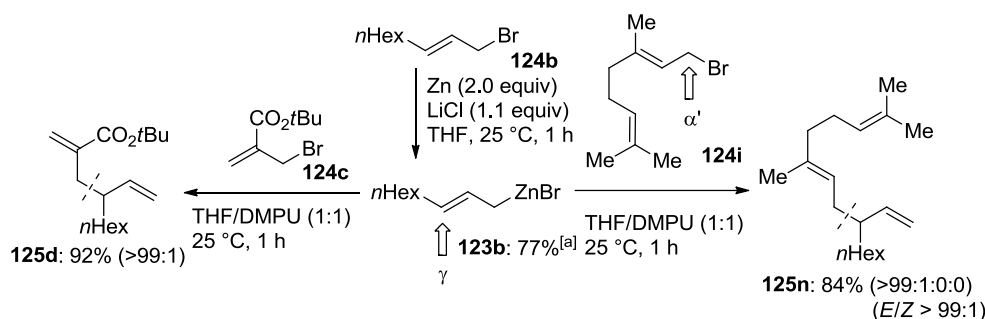


Figure 5: Set of 17 polyfunctional aryl, benzyl and heteroarylzinc pivalates prepared on a 7.0 mmol scale. Complexed $\text{Mg}(\text{OPiv})\text{X}$ ($\text{X}=\text{Cl}, \text{Br}, \text{I}$) and LiCl are omitted for clarity.

6.4 Regioselective Transition-Metal-Free Allyl–Allyl Cross-Couplings

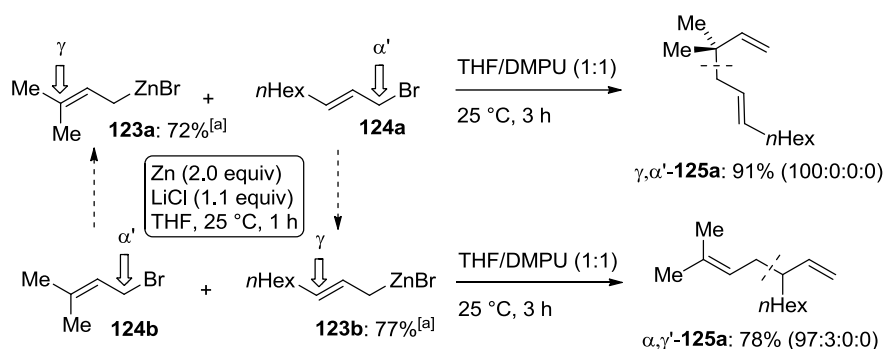
Readily prepared allylic zinc halides undergo $\text{S}_{\text{N}}2$ -type substitutions with allylic bromides in a 1:1 mixture of THF and DMPU providing 1,5-dienes regioselectively. The allylic zinc species reacts at the

most branched end (γ -position) of the allylic system furnishing exclusively γ,α' -allyl-allyl cross-coupling products (Scheme 45). Several functional groups (ester, nitrile) are tolerated. DFT calculations show the importance of lithium chloride in this substitution.



Scheme 45: Allyl-allyl cross-coupling leading to the γ,α' -products of type **125** with full retention of the double bond configuration. (values in parentheses represent the $\gamma,\alpha'/\alpha,\alpha'/\alpha,\gamma'/\gamma,\gamma'$ ratio) [a] LiCl is omitted for clarity.

Furthermore, by inverting the polarity of the reagents, we were also able to prepare selectively the corresponding α,γ' -regioisomer (Scheme 46).



Scheme 46: Transition-metal-free allyl-allyl cross-coupling leading to the γ,α' -products of type **125** after 3 h at room temperature in very high selectivity. [a] LiCl is omitted for clarity. Yield determined by titration with I_2 .

Remarkably, the double bond stereochemistry of the allylic halide is maintained during the cross-coupling process. This cross-coupling of allylic zinc reagents can be extended to propargylic and benzylic halides (Figure 6).

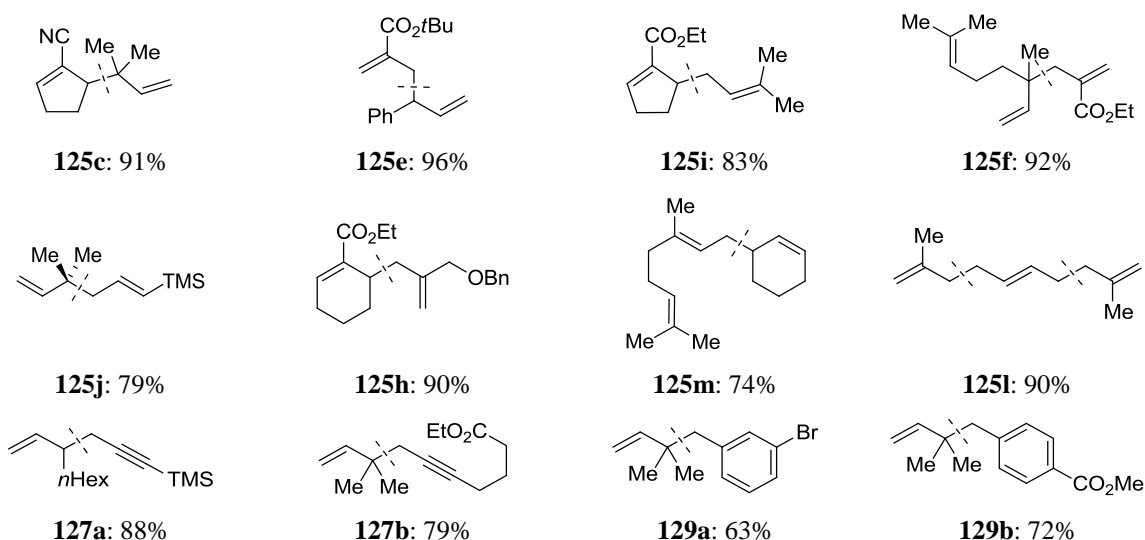
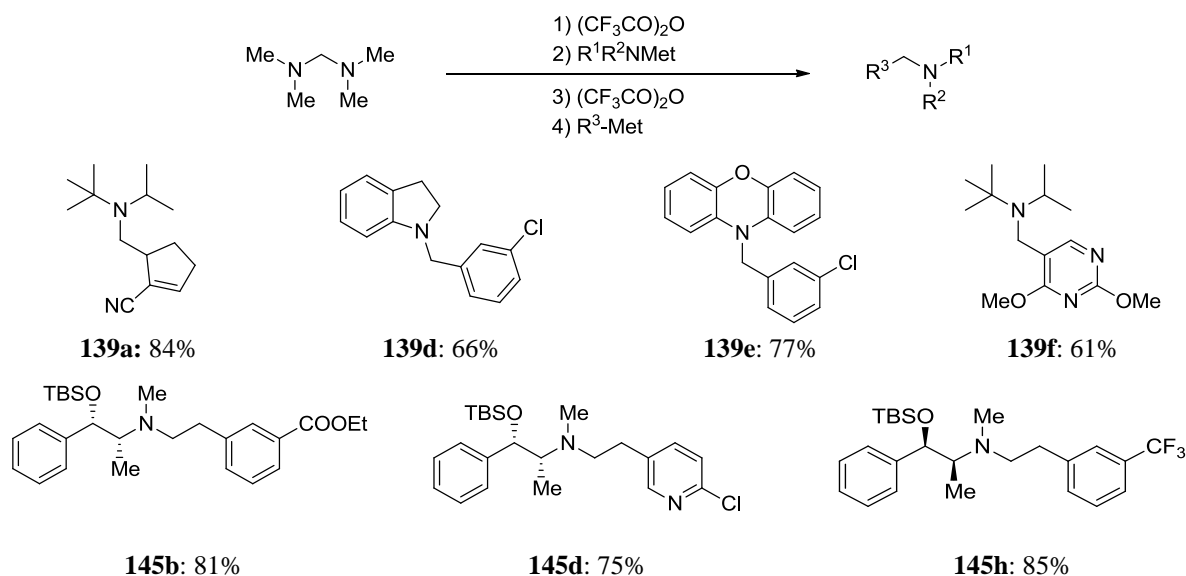


Figure 6: Selected examples of cross-couplings in a 1:1 mixture of THF and DMPU within 1-3 h at 25 °C.

6.5 Preparation of Tertiary Amines by the Reaction of Iminium Ions Derived from Unsymmetrical Aminals with Zinc and Magnesium Organometallics

An efficient method for the preparation of new polyfunctional iminium salts was developed. The resulting compounds gave access to a wide range of valuable tertiary amines via a one-pot reaction with benzyl-, aryl-, and allylzinc reagents (Scheme 47). Moreover, this homologative amination procedure allowed the conversion of ephedrine derivatives to the corresponding benzylic and phenethylic amines which showed a promising structure for biological evaluation.



Scheme 47: Preparation of tertiary amines by cleavage of mixed aminals **134** to mixed iminium ions **135** and subsequent reaction with organometallic reagents.

C. EXPERIMENTAL PART

1 General Considerations

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. AcOEt was purchased from Sigma-Aldrich with a purity of 99% and used without distillation or drying prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ¹H-NMR (25 °C) and capillary GC.

1.1 Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

CH₂Cl₂ was predried over CaCl₂ and distilled from CaH₂.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Et₂O was predried over CaH₂ and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

Pyridine was dried over KOH and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and then stored over molecular sieves.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acyl chlorides were distilled prior to use.

***i*PrMgCl·LiCl** solution in THF was obtained from Rockwood Lithium.

***n*BuLi** solution in hexane was obtained from Rockwood Lithium.

TMPMgCl·LiCl (17) was prepared according to a literature procedure.¹⁰⁵

Zinc dust (> 98%) was obtained from Sigma Aldrich. MgBu₂ was purchased from Rockwood Lithium.

All reagents not listed in the supporting information were obtained from commercial sources. Liquid aldehydes and acid chlorides were distilled prior to use.

¹⁰⁵ a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) T. Kunz, P. Knochel, *Angew. Chem.* **2012**, *124*, 1994; *Angew. Chem. Int. Ed.* **2012**, *51*, 1958.

1.3 Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in THF.¹⁰⁶

Organolithium reagents were titrated against isopropanol using 1,10-phenanthroline as indicator in THF.¹⁰⁷

TMPMgCl·LiCl (17) was titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck.

Thin layer chromatography was performed using SiO_2 pre-coated aluminum plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- Seebach's stain (aka "Magic"): Phosphomolybdic acid (2.5 g), $Ce(SO_4)_2$ (1.0 g), conc. H_2SO_4 (6 mL), H_2O (94 mL).

- $KMnO_4$ stain: $KMnO_4$ (3.0 g), K_2CO_3 (20 g), 5% NaOH solution (5 mL), water (300 mL).

1.5 Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments in $CDCl_3$ or C_6D_6 and chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Mass spectroscopy: High resolution (HR-MS) electron impact ionization (EI) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. EI was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) spectra were recorded on a FINNIGAN LTQ FTICR instrument. GCs were recorded on machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm).

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSamplIR II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1}).

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

¹⁰⁶ For a titration method of zinc organometallics, see: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890; As LiCl is already embedded in the organozinc materials, neat THF instead of a 0.5 M solution of LiCl in THF can be used as the titration medium

¹⁰⁷ H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, 24, 2503.

2 Preparation of Solid, Substituted Allylic Zinc Reagents and Their Reactions with Electrophiles

2.1 Titration of Organozinc Reagents Using Iodine

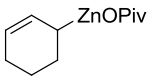
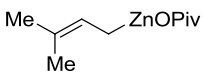
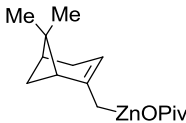
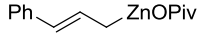
Accurately weighted aliquots (350 mg) of the crude organozinc material were dissolved in dry THF, so that the total volume of the solution was 2 mL. To the solution thus formed, was added a standard solution of iodine (1 M, in dry THF) until the complete appearance of the dark brown color of iodine. Thus, the concentration of the active species (in mmol/g) is determined and thereof the yield of the insertion.¹⁰⁶

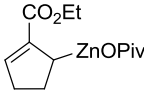
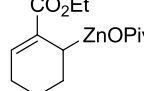
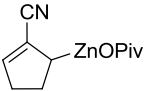
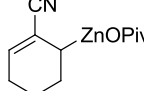
2.2 Stability Studies of Allylzinc Reagents under Argon

To evaluate the stability of organozinc reagents under argon, accurately weighed aliquots of the solid material were placed in Schlenk-flasks at 25 °C. After an extended period of time under argon at the given temperature the solid material was dissolved in THF and the resulting solution was titrated against iodine, according to the procedure described above and the measured concentration was compared to the one before the storage. The stability of the allylzinc pivalates is presented in Table 9.

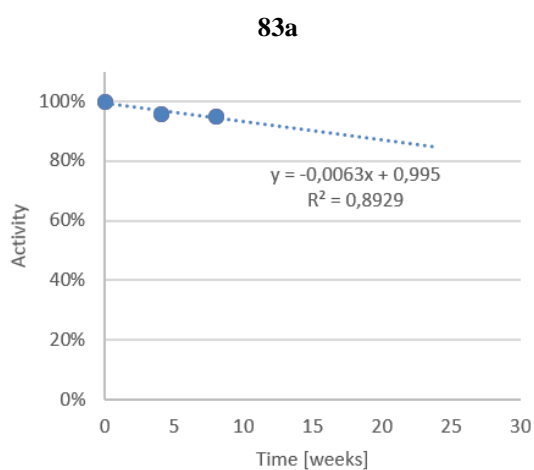
2.3 Stability of Allylzinc Pivalates after Storage under Argon at Room Temperature

Table 9: Stability of allylzinc pivalates after storage under argon at room temperature

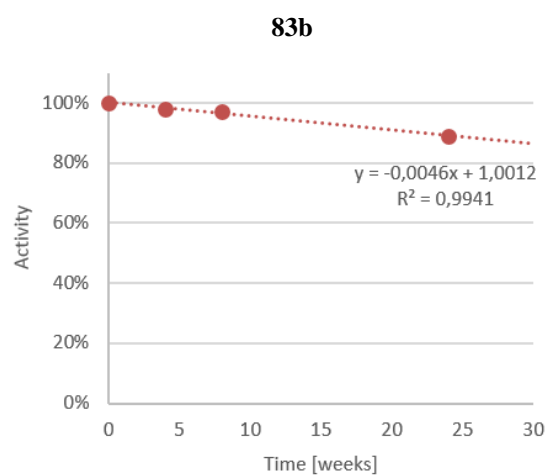
				
	83a	83b	83c	83d
time	Percentage of the remaining active allylzinc species ^a			
4 weeks	96	98	100	100
2 months	95	97 89 ^b	98	100

				
	83e	83f	83g	83h
1 week	Percentage of the remaining active allylzinc species ^a			
1 week			90	
4 weeks	89	86	48	70
2 months	82 ^c	76	25	61

[a] Determined by titration with a stock solution of iodine; [b] titration after 6 months; [c] titration after 6 weeks.



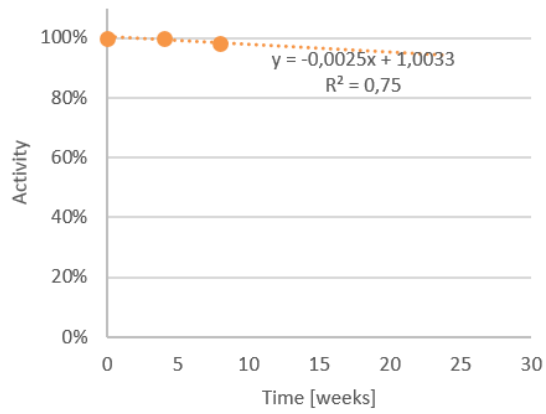
$t_{1/2} = 18$ months



$t_{1/2} = 25$ months

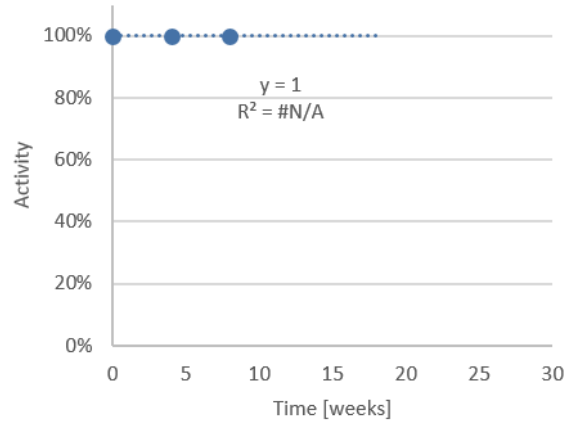
83c

83d



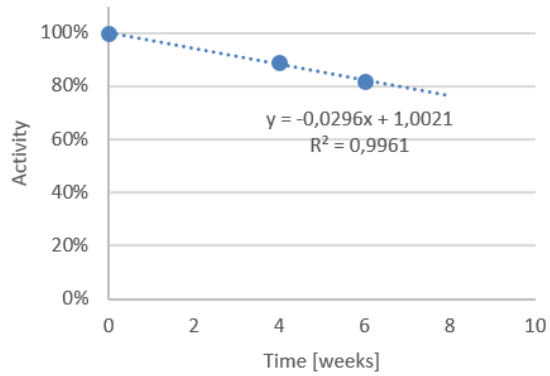
$t_{1/2} > 2$ years

83e



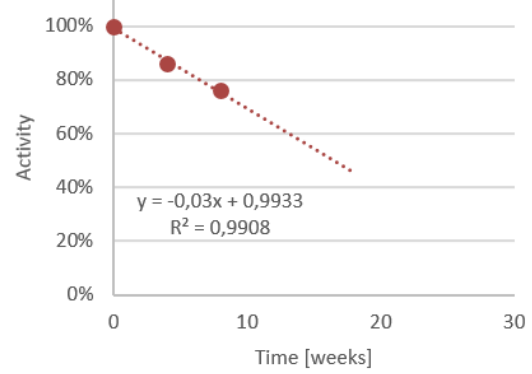
$t_{1/2} > 2$ years

83f



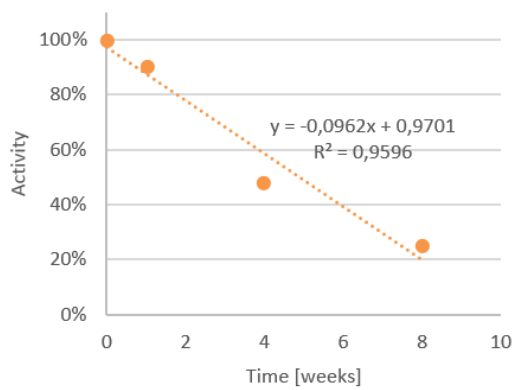
$t_{1/2} = 17$ weeks

83g

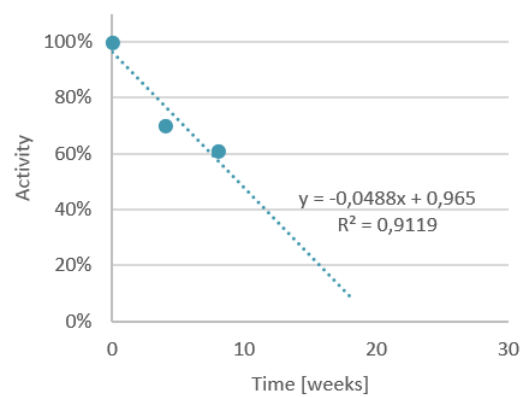


$t_{1/2} = 16$ weeks

83h



$t_{1/2} = 33$ days



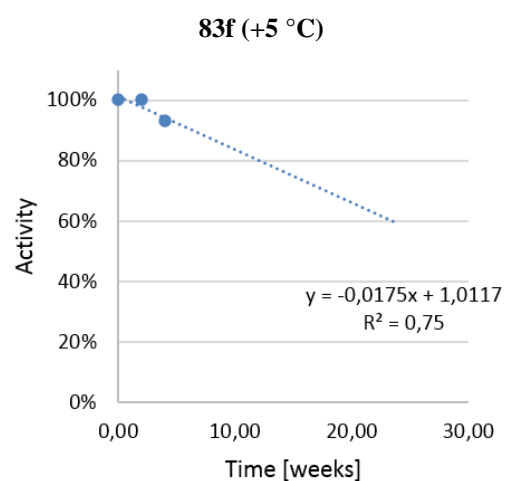
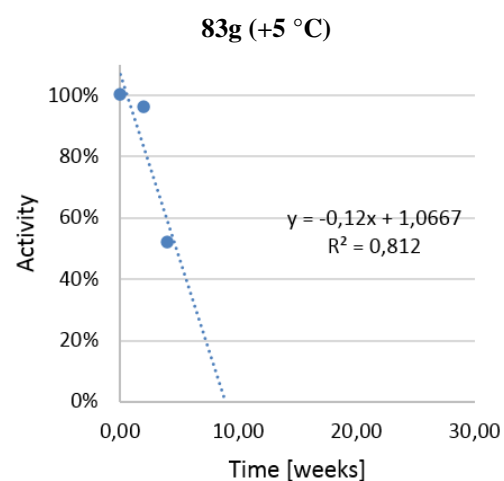
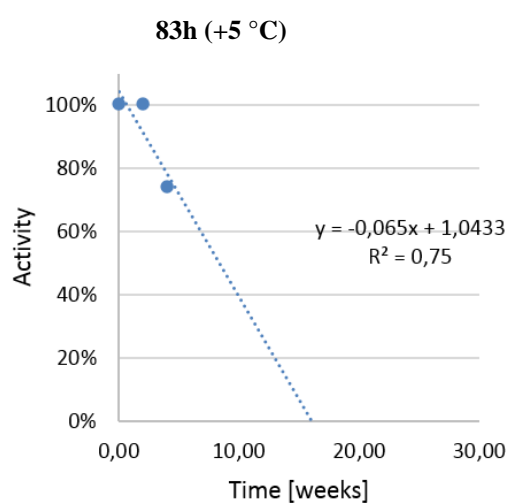
$t_{1/2} = 59$ days

2.4 Stability Tests after Storage under Argon at +5 °C

Table 10: Stability tests after storage under argon at +5 °C

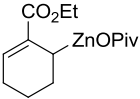
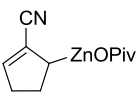
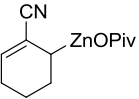
	<chem>CCOC(=O)C1=CC=CC=C1ZnOP(=O)(O)O</chem> 83f	<chem>N#CC1=CC=CC=C1ZnOP(=O)(O)O</chem> 83g	<chem>N#CC1=CC=CC=C1ZnOP(=O)(O)O</chem> 83h
time	Percentage of the remaining active allylzinc species ^a		
1 week	n.d.	n.d.	n.d.
2 weeks	100	96	100
1 month	93	52	74

[a] Determined by titration with a stock solution of iodine.

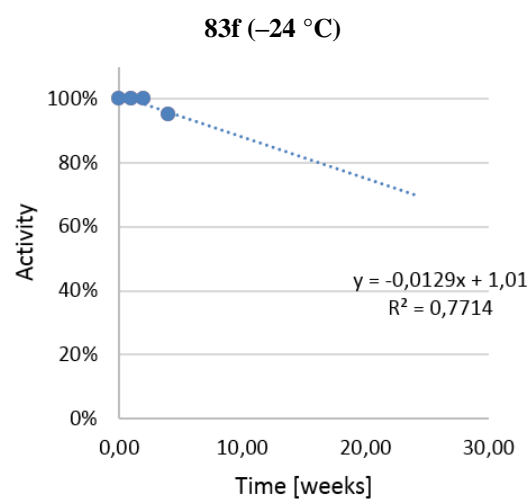
 $t_{1/2} = 29$ weeks $t_{1/2} = 33$ days $t_{1/2} = 58$ days

2.5 Stability Tests after Storage under Argon at -24 °C

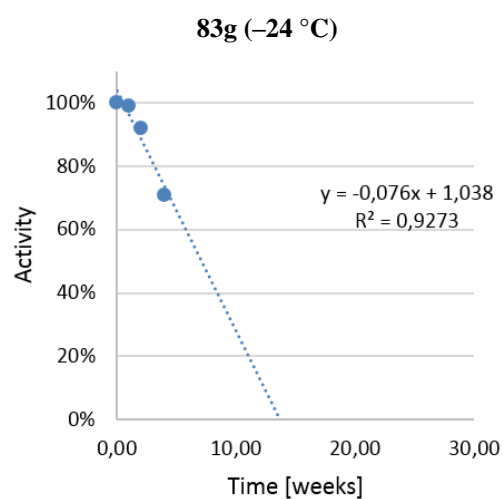
Table 11: Stability Tests after Storage under Argon at -24 °C

	 83f	 83g	 83h
time	Percentage of the remaining active allylzinc species ^a		
1 week	100	99	100
2 weeks	100	92	98
1 month	95	71	91

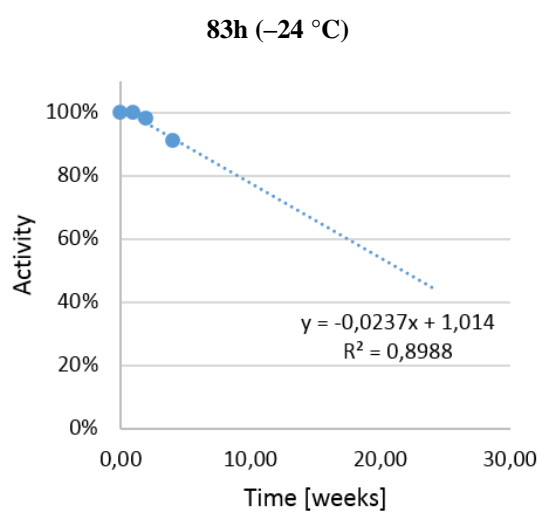
[a] Determined by titration with a stock solution of iodine.



$t_{1/2} = 40$ weeks

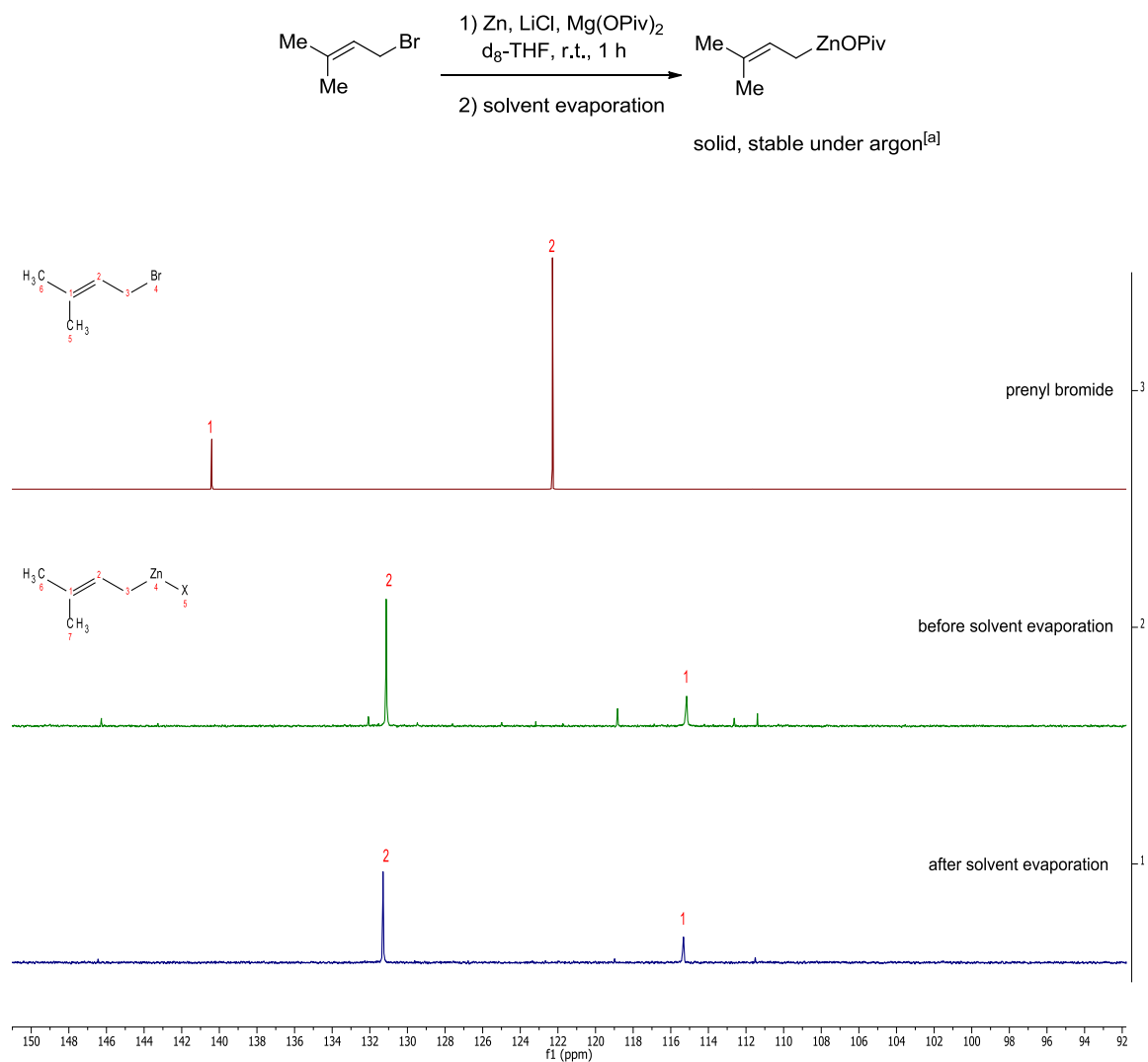


$t_{1/2} = 50$ days



$t_{1/2} = 152$ days

2.6 NMR-Spectra of Prenylzinc Pivalate Before and After Solvent Evaporation



Scheme 48: NMR-Spectra of prenylzinc pivalate (**83b**) before and after solvent evaporation. Region 92–150 ppm is shown for clarity. [a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity.

2.7 Catalyst Evaluation for the Pd-Catalyzed Cross-Coupling

Table 12: Catalyst Evaluation for the Pd-Catalyzed Cross-Coupling^[a]

entry	catalyst	conversion	desired product	Ar-Ar
1	Pd(OAc) ₂ / SPhos	2 / 4 mol%	0	6
2	Pd(OAc) ₂ / dppp	2 / 4 mol%	0	0
3	Pd(dba) ₂ / TFP	2 / 4 mol%	18	2
4	PEPPSI-IPr	2 mol%	14	1
5	PEPPSI-IPent	2 mol%	92 (90) ^[c]	2
6	Pd(PPh ₃) ₄	4 mol%	0	0

[a] (2-Cyanocyclopent-2-en-1-yl)zinc pivalate (**83g**, 0.5 mmol) and 3-bromothiophene (**85h**, 0.4 mmol) were used.

[b] Determined by GC with undecane (C₁₁H₂₄) used as an internal standard. [c] Yield of isolated product.

2.8 Preparation of Starting Materials

Compounds **84d**,¹⁰⁸ **84e**,¹⁰⁹ **84f**,¹¹⁰ **84g**,¹¹⁰ **84h**,¹¹¹ and **88e**¹¹² were prepared according to literature known procedures.

2.9 Preparation of Mg(OPiv)₂

Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, and dissolved in dry THF (100 mL). The solution was cooled to 0 °C and dibutylmagnesium (148 mL, 1.49 M in hexane, 220 mmol) was added over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring continued at 25 °C for 6 additional hours at which point bubbling was ceased (a white precipitation was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least four additional hours. Mg(OPiv)₂ was received in quantitative yield, as a puffy amorphous white solid.

¹⁰⁸ P. E. Peterson, G. Grant, *J. Org. Chem.* **1991**, 56, 16.

¹⁰⁹ Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, 49, 8516.

¹¹⁰ C. Sämann, P. Knochel, *Synthesis* **2013**, 1870.

¹¹¹ J.-B. Langlois, A. Alexakis, *Adv. Synth. Catal.* **2010**, 352, 447.

¹¹² Y. Y. Novikov, P. Sampson, *Org. Lett.* **2003**, 5, 2263.

2.10 Typical Procedures

Typical Procedure for the Preparation of the Solid Allylzinc Pivalates of Type 83 (TP1):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and LiCl (466 mg, 11.0 mmol). The mixture was dried with a heat gun (330 °C, 10 min) under high vacuum followed by the addition of zinc dust (1.31 g, 20.0 mmol). The vessel was evacuated and refilled with argon. THF (10 mL) and 1,2-dibromoethane (215 μL , 2.50 mmol) were added via syringe and the reaction mixture was heated to 50 °C until bubbling occurred. The allylic halide (10.0 mmol) was added as a solution in THF (10 mL) over a period of 30 min using a syringe pump. The mixture was stirred for the given time at room temperature before the zinc powder was allowed to settle down. The supernatant solution was carefully filtrated using a syringe filter and the solvent was removed *in vacuo* to yield the corresponding zinc pivalate of type 1 as a solid. The yield for the insertion was determined by iodometric titration.

Typical Procedure for the Cross-Coupling of the Allylzinc Pivalates of Type 83 with Aryl Bromides of Type 85 (TP2):

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent (1.0 equiv) was dissolved in dry THF or the previously solved organozinc solution was added via syringe. PEPPSI-IPent (2 mol%) and the aryl bromide (0.80 equiv) were added and the mixture was stirred for 4 h at 50 °C. Then NH_4Cl solution (5 mL, sat. aq.) was added, the aqueous layer was extracted with EtOAc (3 \times 10 mL), washed with solutions of NaHCO_3 (5 mL, sat. aq.), and NaCl (5 mL, sat. aq.) and the combined organic phases were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

Typical Procedure for the Addition of the Allylzinc Pivalates of Type 83 to Aldehydes and Methyl Ketones of Type 88 (TP3):

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent (1.0 equiv) was dissolved in dry THF or the previously solved organozinc solution was added via syringe. The solution was cooled to -78 °C and the carbonyl compound was added was added and the mixture was stirred 1 h at -78 °C. Then NH_4Cl solution (5 mL, sat. aq.) was added, the aqueous layer was extracted with EtOAc (3 \times 10 mL), washed with solutions of NaHCO_3 (5 mL, sat. aq.) and NaCl (5 mL, sat. aq.) and the combined organic phases were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

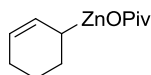
Typical Procedure for the Reaction of the Allylzinc Pivalates of Type 83 to Acid Chlorides of Type 91 (TP4):

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the solid organozinc reagent (1.0 equiv) was dissolved in dry THF or the previously solved organozinc solution was added via syringe. The solution was cooled to -78 °C and the acid chloride was added was added

and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$. Then NH_4Cl solution (5 mL, sat. aq.) was added, the aqueous layer was extracted with EtOAc ($3 \times 10\text{ mL}$), washed with solutions of NaHCO_3 (5 mL, sat. aq.) and NaCl (5 mL, sat. aq.) and the combined organic phases were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products.

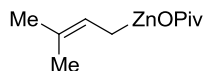
2.11 Preparation of Allylzinc Pivalates

Cyclohex-2-en-1-ylzinc pivalate (83a)



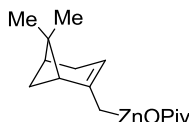
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and THF (10 mL) was added 3-bromocyclohex-1-ene (1.61 g, 10.0 mmol) in THF (10 mL). After 1 h at $25\text{ }^{\circ}\text{C}$ and subsequent filtration and evaporation of the solvent cyclohex-2-en-1-ylzinc pivalate was obtained as a colorless solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.08 mmol/g, which corresponds to a yield of 67% was determined.

Prenylzinc pivalate (83b)



According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and THF (10 mL) was added prenylbromide (1.49 g, 10.0 mmol) in THF (10 mL). After 1 h at $25\text{ }^{\circ}\text{C}$ and subsequent filtration and evaporation of the solvent prenylzinc pivalate was obtained as a colorless solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.01 mmol/g, which corresponds to a yield of 74% was determined.

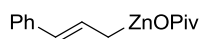
Myrtenylzinc pivalate (83c)



According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and THF (10 mL) was added myrtenylbromide (2.15 g, 10.0 mmol) in THF (10 mL). After 1 h at $25\text{ }^{\circ}\text{C}$ and subsequent filtration and evaporation of the solvent myrtenylzinc pivalate was obtained as a colorless solid. The content of active zinc species was determined by titration

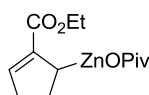
with a stock solution of iodine (1.00 M in THF). A concentration of 0.96 mmol/g, which corresponds to a yield of 77% was determined.

Cinnamylzinc pivalate (83d)



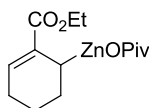
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), Mg(OPiv)₂ (2.72 g, 12.0 mmol) and THF (10 mL) was added cinnamylchloride (1.52 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration and evaporation of the solvent cinnamylzinc pivalate was obtained as a colorless solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.95 mmol/g, which corresponds to a yield of 78% was determined.

(2-(Ethoxycarbonyl)cyclopent-2-en-1-yl)zinc pivalate (83e)

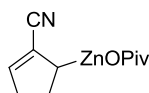


According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), Mg(OPiv)₂ (2.72 g, 12.0 mmol) and THF (10 mL) was added ethyl 5-chlorocyclopent-1-enecarboxylate (1.75 g, 10.0 mmol) in THF (10 mL). After 3 h at 25 °C and subsequent filtration and evaporation of the solvent (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc pivalate was obtained as a yellow solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.97 mmol/g, which corresponds to a yield of 51% was determined.

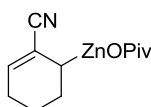
(2-(Ethoxycarbonyl)cyclohex-2-en-1-yl)zinc pivalate (83f)



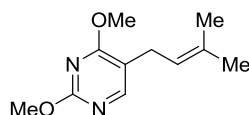
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), Mg(OPiv)₂ (2.72 g, 12.0 mmol) and THF (10 mL) was added ethyl 6-chlorocyclohex-1-enecarboxylate (1.89 g, 10.0 mmol) in THF (10 mL). After 3 h at 25 °C and subsequent filtration and evaporation of the solvent (2-(ethoxycarbonyl)cyclohex-2-en-1-yl)zinc pivalate was obtained as a yellow solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.23 mmol/g, which corresponds to a yield of 90% was determined.

(2-Cyanocyclopent-2-en-1-yl)zinc pivalate (83g)

According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), Mg(OPiv)₂ (2.72 g, 12.0 mmol) and THF (10 mL) was added 5-bromocyclopent-1-enecarbonitrile (1.72 g, 10.0 mmol) in THF (10 mL). After 3 h at 25 °C and subsequent filtration and evaporation of the solvent (2-cyanocyclopent-2-en-1-yl)zinc pivalate was obtained as a dark yellow solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.04 mmol/g, which corresponds to a yield of 81% was determined.

(2-Cyanocyclohex-2-en-1-yl)zinc pivalate (83h)

According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol), Mg(OPiv)₂ (2.72 g, 12.0 mmol) and THF (10 mL) was added 6-chlorocyclohex-1-enecarbonitrile (1.41 g, 10.0 mmol) in THF (10 mL). After 3 h at 25 °C and subsequent filtration and evaporation of the solvent (2-cyanocyclohex-2-en-1-yl)zinc pivalate was obtained as a yellow solid. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 1.00 mmol/g, which corresponds to a yield of 55% was determined.

2.12 Preparation of Cross-Coupling Products of Type 86**2,4-Dimethoxy-5-(3-methylbut-2-en-1-yl)pyrimidine (86a)**

According to **TP2** prenylzinc pivalate in dry THF (0.38 M, 3.12 mL, 1.20 mmol) was added to 5-bromo-2,4-dimethoxypyrimidine (219 mg, 1.00 mmol) and PEPPSI-IPent (16 mg, 0.02 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a colorless oil (160 mg, 0.77 mmol, 77%).

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 6.20 (s, 1H), 5.40–5.30 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.32 (d, *J* = 7.3 Hz, 2H), 1.76 (s, 3H), 1.68 (s, 3H).

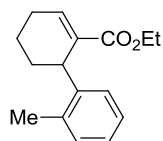
¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 172.4, 172.1, 165.4, 135.0, 119.6, 99.3, 54.7, 53.8, 36.4, 25.9, 18.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3185, 2982, 2955, 2871, 1584, 1559, 1478, 1457, 1376, 1346, 1282, 1202, 1146, 1097, 1058, 1038, 1007, 9834, 933, 827, 786, 713, 663.

MS (EI, 70 eV): m/z (%) = 208 (M⁺, 73), 193 (100), 177 (20), 167 (46), 154 (11), 135 (10), 125 (11), 106 (8), 93 (9), 82 (8), 72 (10).

HRMS (EI): m/z calc. for [C₁₁H₁₆N₂O₂]: 208.1212; found: 208.1196 (M⁺).

Ethyl 2'-methyl-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (86b)



According to **TP2** (2-(ethoxycarbonyl)cyclohex-2-en-1-yl)zinc pivalate in dry THF (0.40 M, 1.25 mL, 0.50 mmol) was added to 3-bromotoluene (68 mg, 0.40 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 30:1) afforded the title compound as a colorless oil (77 mg, 0.32 mmol, 79%).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.26–7.21 (m, 1H), 7.18–7.11 (m, 1H), 7.11–7.02 (m, 2H), 7.00–6.91 (m, 1H), 4.15–4.06 (m, 1H), 4.07–3.90 (m, 2H), 2.42 (s, 3H), 2.38–2.15 (m, 2H), 1.73–1.45 (m, 3H), 1.05 (t, J = 7.1 Hz, 3H).

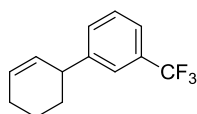
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 167.3, 143.2, 141.0, 135.5, 133.1, 130.5, 127.1, 126.0, 125.6, 60.2, 35.8, 29.2, 26.0, 19.5, 17.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2936, 2867, 1712, 1692, 1647, 1603, 1488, 1463, 1446, 1424, 1390, 1369, 1344, 1288, 1238, 1168, 1146, 1096, 1081, 1059, 1018, 974, 932, 915, 882, 862, 842, 782, 756, 728, 699.

MS (EI, 70 eV): m/z (%) = 244 (M⁺, 50), 198 (100), 183 (75), 170 (42), 155 (25), 141 (33), 128 (35), 115 (27), 105 (23), 91 (17), 79 (15).

HRMS (EI): m/z calc. for [C₁₆H₂₀O₂]: 244.1463; found: 244.1456 (M⁺).

3'-(Trifluoromethyl)-1,2,3,4-tetrahydro-1,1'-biphenyl (86c)



According to **TP2** cyclohex-2-en-1-ylzinc pivalate in dry THF (0.31 M, 1.60 mL, 0.50 mmol) was added to 1-bromo-3-(trifluoromethyl)benzene (90 mg, 0.40 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in

THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a colorless oil (65 mg, 0.29 mmol, 72%).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.50–7.43 (m, 2H), 7.43–7.37 (m, 2H), 6.00–5.89 (m, 1H), 5.75–5.64 (m, 1H), 3.54–3.40 (m, 1H), 2.19–1.92 (m, 3H), 1.85–1.44 (m, 3H).

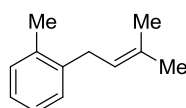
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 147.7, 131.3 (q, J = 1.4 Hz), 130.7 (d, J = 31.9 Hz), 129.4, 129.3, 128.8, 124.6 (q, J = 3.8 Hz), 124.5 (d, J = 272.3 Hz), 123.0 (q, J = 3.9 Hz), 41.8, 32.7, 25.1, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3406, 2943, 2876, 1658, 1613, 1491, 1435, 1327, 1230, 1163, 1118, 1098, 1072, 1001, 960, 891, 800, 760, 696, 678, 654.

MS (EI, 70 eV): m/z (%) = 226 (M⁺, 100), 211 (61), 198 (18), 185 (10), 172 (25), 157 (11), 142 (9), 129 (65), 115 (10).

HRMS (EI): m/z calc. for [C₁₃H₁₃F₃]: 226.0969; found: 266.0955 (M⁺).

1-Methyl-4-(3-methylbut-2-en-1-yl)benzene (86d)



According to **TP2** prenylzinc pivalate in dry THF (0.38 M, 2.60 mL, 1.00 mmol) was added to 2-bromotoluene (136 mg, 0.80 mmol) and PEPPSI-IPent (16 mg, 0.02 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a colorless oil (90 mg, 0.56 mmol, 70%).

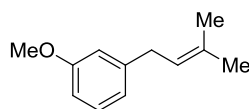
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.22–7.08 (m, 4H), 5.34–5.22 (m, 1H), 3.34 (d, J = 7.3 Hz, 2H), 2.33 (s, 3H), 1.81–1.71 (m, 6H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 140.1, 136.3, 132.5, 130.2, 128.7, 126.1, 126.0, 122.7, 32.3, 25.9, 19.6, 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3414, 3066, 2974, 2930, 1716, 1603, 1576, 1491, 1459, 1380, 1286, 1251, 1220, 1160, 1142, 1075, 1052, 905, 863, 739, 692.

MS (EI, 70 eV): m/z (%) = 160 (M⁺, 57), 145 (100), 130 (22), 117 (18), 104 (23), 91 (13), 77 (8).

HRMS (EI): m/z calc. for [C₁₂H₁₆]: 160.1252; found: 160.1245 (M⁺).

1-Methoxy-3-(3-methylbut-2-en-1-yl)benzene (86e)

According to **TP2** prenylzinc pivalate in dry THF (0.38 M, 2.60 mL, 1.00 mmol) was added to 3-bromoanisole (150 mg, 0.80 mmol) and PEPPSI-IPent (16 mg, 0.02 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 80:1) afforded the title compound as a colorless oil (100 mg, 0.57 mmol, 71%).

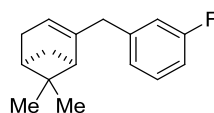
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.26–7.14 (m, 1H), 6.84–6.67 (m, 3H), 5.41–5.25 (m, 1H), 3.80 (s, 3H), 3.38–3.27 (m, 2H), 1.80–1.66 (m, 6H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 159.8, 143.6, 132.8, 129.4, 123.1, 120.9, 114.3, 111.1, 55.3, 34.5, 25.9, 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3055, 3000, 2937, 2834, 1597, 1573, 1475, 1464, 1410, 1290, 1278, 1231, 1202, 1168, 1091, 1055, 1046, 1029, 992, 908, 872, 851, 799, 771, 693.

MS (EI, 70 eV): m/z (%) = 176 (M⁺, 88), 161 (100), 146 (16), 129 (13), 121 (24), 115 (14), 108 (11), 91 (24), 77 (9).

HRMS (EI): m/z calc. for [C₁₂H₁₆O]: 176.1201; found: 176.1186 (M⁺).

(1R,5S)-2-(3-Fluorobenzyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (86f)

According to **TP2** (–)-myrtenylzinc pivalate in dry THF (0.32 M, 1.88 mL, 0.60 mmol) was added to 1-bromo-3-fluorobenzene (77 mg, 0.50 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (89 mg, 0.39 mmol, 77%).

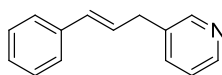
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.2–7.1 (m, 1H), 6.9–6.8 (m, 1H), 6.8–6.7 (m, 2H), 5.2–5.2 (m, 1H), 3.3–3.1 (m, 2H), 2.3–2.1 (m, 4H), 2.1–2.0 (m, 1H), 1.9 (td, J = 5.6, 1.5 Hz, 1H), 1.1 (s, 3H), 0.7 (s, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 163.0 (d, J = 244.9 Hz), 146.8, 142.4 (d, J = 7.1 Hz), 129.5 (d, J = 8.2 Hz), 124.9 (d, J = 2.7 Hz), 118.4, 116.1 (d, J = 20.9 Hz), 112.9 (d, J = 21.1 Hz), 45.6, 43.4 (d, J = 1.7 Hz), 40.8, 38.0, 32.0, 31.5, 26.3, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2984, 2916, 2833, 1615, 1588, 1487, 1469, 1446, 1382, 1366, 1266, 1250, 1221, 1204, 1135, 1074, 982, 949, 930, 886, 872, 806, 774, 744, 711, 701, 680.

MS (EI, 70 eV): m/z (%) = 230 (M⁺, 12), 215 (5), 186 (61), 173 (7), 159 (10), 147 (10), 133 (9), 121 (15), 109 (100), 91 (27), 79 (12), 65 (3).

HRMS (EI): m/z calc. for [C₁₆H₁₉F]: 230.1471; found: 230.1461 (M⁺).

3-Cinnamylpyridine (86g)

According to **TP2** cinnamylzinc pivalate in dry THF (0.57 M, 0.88 mL, 0.50 mmol) was added to 3-bromopyridine (69 mg, 0.40 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (56 mg, 0.29 mmol, 72%).

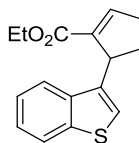
¹H-NMR (400 MHz, benzene-d₆): δ / ppm = 8.6–8.5 (m, 1H), 8.5–8.4 (m, 1H), 7.2–7.1 (m, 4H), 7.1–6.9 (m, 2H), 6.8–6.6 (m, 1H), 6.3–6.1 (m, 1H), 6.0–5.9 (m, 1H), 3.1–3.0 (m, 2H).

¹³C-NMR (101 MHz, benzene-d₆): δ / ppm = 150.8, 148.3, 137.6, 135.6, 135.5, 132.2, 128.8, 128.1, 127.6, 126.6, 123.3, 36.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3028, 2958, 2924, 1679, 1596, 1578, 1557, 1495, 1479, 1449, 1424, 1372, 1272, 1190, 1125, 1103, 1076, 1045, 1027, 1002, 967, 920, 745, 693.

MS (EI, 70 eV): m/z (%) = 195 (100, M⁺), 180 (17), 167 (14), 139 (6), 115 (17), 91 (12), 77 (6).

HRMS (EI): m/z calc. for [C₁₄H₁₃N]: 195.2597; found: 195.1034 (M⁺).

Ethyl 5-(Benzo[*b*]thiophen-3-yl)cyclopent-1-enecarboxylate (86h)

According to **TP2** (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc pivalate in dry THF (0.20 M, 3.00 mL, 0.60 mmol) was added to 3-bromobenzo[*b*]thiophene (107 mg, 0.50 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (80 mg, 0.38 mmol, 75%).

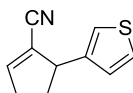
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.92–7.75 (m, 2H), 7.45–7.30 (m, 2H), 7.12–7.03 (m, 1H), 6.94 (s, 1H), 4.63–4.50 (m, 1H), 4.17–4.02 (m, 2H), 2.76–2.43 (m, 3H), 2.11–1.95 (m, 1H), 1.11 (t, J = 7.1 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 164.9, 145.3, 141.0, 139.2, 138.7, 138.6, 124.3, 123.9, 123.0, 122.1, 120.6, 60.3, 43.6, 32.4, 32.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3064, 2978, 2937, 2902, 1712, 1630, 1459, 1428, 1391, 1369, 1339, 1299, 1277, 1257, 1244, 1229, 1193, 1178, 1158, 1144, 1096, 1079, 1048, 1031, 1020, 946, 926, 883, 860, 763, 733, 716, 693.

MS (EI, 70 eV): m/z (%) = 272 (42, M⁺), 243 (24), 225 (42), 198 (91), 183 (61), 171 (100), 158 (30), 147 (27), 134 (61), 115 (42), 102 (12), 89 (18).

HRMS (EI): m/z calc. for [C₁₆H₁₆O₂S]: 272.0871; found: 272.0864 (M⁺).

5-(Thiophen-3-yl)cyclopent-1-enecarbonitrile (86i)

According to **TP2** (2-cyanocyclopent-2-en-1-yl)zinc pivalate in dry THF (0.30 M, 1.67 mL, 0.50 mmol) was added to 3-bromothiophene (65 mg, 0.40 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (63 mg, 0.36 mmol, 90%).

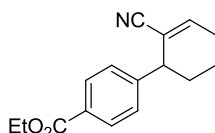
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.32 (ddd, J = 5.0, 2.9, 0.4 Hz, 1H), 7.08 (ddd, J = 3.0, 1.4, 0.7 Hz, 1H), 6.96 (ddd, J = 5.0, 1.3, 0.3 Hz, 1H), 6.82–6.77 (m, 1H), 4.27–4.12 (m, 1H), 2.80–2.57 (m, 2H), 2.57–2.40 (m, 1H), 2.07–1.90 (m, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 149.4, 142.4, 126.7, 126.5, 121.1, 118.8, 116.4, 47.8, 33.0, 32.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3400, 3103, 2945, 2842, 2218, 1714, 1611, 1514, 1454, 1432, 1416, 1389, 1365, 1321, 1288, 1234, 1200, 1166, 1134, 1082, 1033, 967, 944, 924, 873, 842, 831, 779, 726, 663.

MS (EI, 70 eV): m/z (%) = 175 (M⁺, 100), 160 (35), 147 (29), 135 (11), 115 (12), 97 (6), 84 (29).

HRMS (EI): m/z calc. for [C₁₀H₉NS]: 175.0456; found: 175.0449 (M⁺).

Ethyl 6'-Cyano-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-4-carboxylate (86j)

According to **TP2** (2-cyanocyclohex-2-en-1-yl)zinc pivalate in dry THF (0.20 M, 3.00 mL, 0.60 mmol) was added to ethyl 4-bromobenzoate (108 mg, 0.50 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a colorless oil (112 mg, 0.44 mmol, 88%).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.06–7.95 (m, 2H), 7.31–7.19 (m, 2H), 6.88 (td, J = 4.0, 1.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.67–3.52 (m, 1H), 2.37–2.20 (m, 2H), 2.14–1.94 (m, 1H), 1.80–1.47 (m, 3H), 1.36 (t, J = 7.1 Hz, 3H).

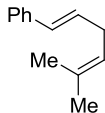
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 166.3, 147.3, 147.1, 130.0, 129.5, 127.8, 118.7, 114.9, 60.9, 42.6, 31.3, 25.9, 18.4, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2940, 2871, 2828, 2216, 1712, 1632, 1610, 1575, 1507, 1447, 1417, 1391, 1366, 1310, 1273, 1180, 1149, 1102, 1080, 1020, 970, 932, 906, 875, 851, 806, 770, 707.

MS (EI, 70 eV): m/z (%) = 255 (21, M^+), 227 (7), 210 (100), 182 (53), 167 (17), 154 (43), 140 (24), 127 (39), 115 (29), 105 (14), 91 (11), 77 (21).

HRMS (EI): m/z calc. for $[C_{16}H_{17}NO_2]$: 255.1259; found: 255.1247 (M^+).

(*E*)-(5-Methylhexa-1,4-dien-1-yl)benzene (86k)



According to **TP2** prenylzinc pivalate in dry THF (0.34 M, 1.76 mL, 0.60 mmol) was added to (*E*)- β -bromostyrene (91.5 mg, 0.50 mmol) and PEPPSI-IPent (8 mg, 0.01 mmol) in THF (0.5 mL) and the mixture was stirred for 4 h at 50 °C. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (70 mg, 0.41 mmol, 81%).

1H -NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32–7.26 (m, 2H), 7.28–7.15 (m, 2H), 7.19–7.07 (m, 1H), 6.32 (dt, J = 15.7, 1.7 Hz, 1H), 6.13 (dt, J = 15.8, 6.5 Hz, 1H), 5.21–5.12 (m, 1H), 2.88–2.80 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H).

^{13}C -NMR (101 MHz, $CDCl_3$): δ / ppm = 138.0, 133.2, 129.7, 129.7, 128.6, 126.9, 126.1, 121.7, 31.8, 25.9, 17.9.

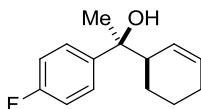
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 3060, 3026, 2968, 2913, 2855, 1672, 1650, 1599, 1578, 1495, 1448, 1376, 1306, 1262, 1206, 1156, 1104, 1074, 1029, 981, 962, 927, 908, 828, 766, 738, 729, 690.

MS (EI, 70 eV): m/z (%) = 172 (46, M^+), 156 (38), 142 (23), 129 (100), 115 (30), 91 (31), 77 (9).

HRMS (EI): m/z calc. for $[C_{13}H_{16}]$: 172.1252; found: 172.1260 (M^+).

2.13 Diastereoselective Preparation of Homoallylic Alcohols of Type 89

(*S*^{*})-1-(4-Fluorophenyl)-1-((*R*^{*})-cyclohex-2-en-1-yl)ethanol (89a)



According to **TP3** cyclohex-2-en-1-ylzinc pivalate (4.29 mL, 0.28 M, 1.20 mmol) was added to a solution of 1-(4-fluorophenyl)ethanone (247 mg, 1.60 mmol) at −78 °C and the mixture was stirred 1 h at −78 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (196 mg, 0.89 mmol, 89%, d.r. > 99:1).

1H -NMR (300 MHz, $CDCl_3$): δ / ppm = 7.46–7.32 (m, 2H), 7.09–6.94 (m, 2H), 5.99–5.85 (m, 1H), 5.82–5.70 (m, 1H), 2.58–2.44 (m, 1H), 2.00–1.89 (m, 2H), 1.79–1.65 (m, 2H), 1.58 (s, 3H), 1.52–1.33 (m, 2H), 1.33–1.16 (m, 1H).

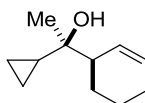
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 161.7 (d, J = 244.6 Hz), 143.0 (d, J = 3.0 Hz), 132.0, 127.0 (d, J = 7.8 Hz), 126.3, 114.7 (d, J = 21.1 Hz), 75.9, 46.8, 28.2, 25.3, 24.5, 22.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3406, 3027, 2933, 2863, 1660, 1601, 1508, 1450, 1408, 1373, 1345, 1306, 1222, 1160, 1112, 1081, 1014, 965, 942, 924, 906, 892, 880, 836, 821, 794, 753, 735, 727, 716.

MS (EI, 70 eV): m/z (%) = 202 (1), 159 (2), 146 (2), 139 (100), 123 (14), 109 (3), 95 (7), 79 (5).

HRMS (EI): m/z calc. for [C₁₄H₁₅F]: 202.1158; found: 202.1132 ([M-H₂O]⁺).

(*R)-1-((*R**)-cyclohex-2-en-1-yl)-1-cyclopropylethanol (89b)**



According to **TP3** cyclohex-2-en-1-ylzinc pivalate (5.30 mL, 0.23 M, 1.20 mmol) was added to a solution of cyclopropyl methyl ketone (84 mg, 1.00 mmol) at -78 °C and the mixture was stirred 1.5 h at -78 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1) afforded the title compound as a colorless oil (95 mg, 0.57 mmol, 92%, d.r. = 94:6).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.90–5.77 (m, 2H), 2.36–2.26 (m, 1H), 2.05–1.94 (m, 2H), 1.94–1.76 (m, 2H), 1.55–1.37 (m, 2H), 1.10 (s, 1H), 1.02 (s, 3H), 1.01–0.90 (m, 1H), 0.47–0.25 (m, 4H).

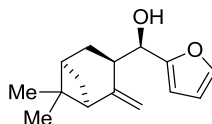
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 129.5, 127.9, 73.3, 47.5, 25.4, 24.5, 23.3, 22.4, 19.3, 1.7, 0.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3448, 3083, 3027, 2971, 2929, 1700, 1684, 1653, 1559, 1576, 1522, 1507, 1456, 1448, 1435, 1371, 1308, 1272, 1254, 1201, 1178, 1141, 1106, 1078, 1050, 1035, 1020, 998, 929, 910, 876, 827, 809, 789, 721, 672, 650.

MS (EI, 70 eV): m/z (%) = 166 (M⁺, 1), 148 (45), 133 (45), 119 (40), 105 (100), 91 (100), 79 (80).

HRMS (EI): m/z calc. for [C₁₁H₁₇]: 149.1330; found: 149.2278 ([M-H₂O]⁺).

(*R*)-((1*R*,3*R*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)(furan-2-yl)methanol (89c)



According to **TP3** (-)-myrtenylzinc pivalate (3.76 mL, 0.32 M, 1.20 mmol) was added to a solution of cyclopropyl methyl ketone (96 mg, 1.00 mmol) at -78 °C and the mixture was stirred 1 h at -78 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a colorless oil (206 mg, 0.89 mmol, 89%, d.r. > 99:1).

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.4 (dd, J = 1.9, 0.9 Hz, 1H), 6.3 (dd, J = 3.3, 1.8 Hz, 1H), 6.3–6.3 (m, 1H), 4.9 (dt, J = 7.9, 1.7 Hz, 2H), 4.5 (dd, J = 9.4, 2.4 Hz, 1H), 3.0–2.9 (m, 1H), 2.9 (d, J

= 2.6 Hz, 1H), 2.5 (t, J = 5.4 Hz, 1H), 2.3–2.2 (m, 1H), 2.0–1.9 (m, 2H), 1.6–1.5 (m, 1H), 1.3 (s, 3H), 1.2 (d, J = 10.3 Hz, 1H), 0.8 (s, 3H).

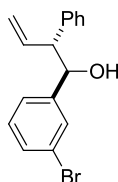
^{13}C -NMR (151 MHz, CDCl_3): δ / ppm = 155.0, 151.7, 142.2, 111.8, 110.3, 108.1, 72.3, 52.5, 41.4, 40.6, 40.3, 27.5, 26.7, 25.9, 21.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3417, 2978, 2918, 2869, 1695, 1635, 1504, 1456, 1383, 1368, 1316, 1262, 1224, 1211, 1186, 1149, 1107, 1076, 1052, 1029, 1009, 956, 941, 930, 920, 884, 841, 807, 731, 702, 689, 656.

MS (EI, 70 eV): m/z (%) = 232 (M^+ , 1), 214 (8), 199 (6), 189 (3), 171 (14), 136 (19), 121 (15), 105 (8), 97 (100), 93 (66), 77 (16).

HRMS (EI): m/z calc. for $[\text{C}_{15}\text{H}_{20}\text{O}_2]$: 232.1463; found: 232.1467 (M^+).

(1R*,2R*)-1-(3-Bromophenyl)-2-phenylbut-3-en-1-ol (89d)



According to **TP3** cinnamylzinc pivalate (1.01 g, 0.95 mmol/g, 0.96 mmol) was solved in 3 mL THF. 3-Bromobenzaldehyde (142 mg, 0.77 mmol) was added at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a colorless oil (201 mg, 0.663 mmol, 86%, d.r. > 99:1).

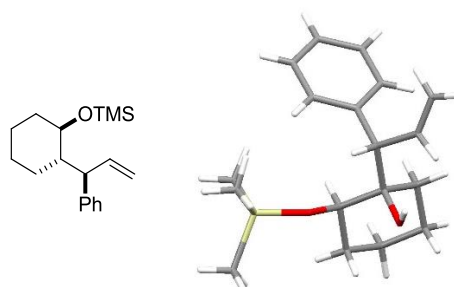
^1H -NMR (300 MHz, CDCl_3): δ / ppm = 7.48–7.10 (m, 5H), 7.10–6.92 (m, 4H), 6.31–6.12 (m, 1H), 5.41–5.14 (m, 2H), 4.79 (d, J = 7.6 Hz, 1H), 3.53–3.42 (m, 1H), 2.33 (s, 1H).

^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 144.1, 140.1, 137.2, 130.4, 129.6, 129.3, 128.5, 128.2, 126.8, 125.4, 122.1, 118.9, 76.5, 59.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3537, 3415, 3062, 3029, 2899, 1684, 1638, 1596, 1570, 1493, 1475, 1453, 1428, 1287, 1184, 1094, 1070, 1032, 996, 920, 849, 783, 757, 728, 696, 674.

MS (EI, 70 eV): m/z (%) = 183 (67), 155 (30), 131 (3), 117 (100), 103 (10), 91 (27), 77 (28), 63 (13), 51 (28).

HRMS (EI): m/z calc. for $[\text{C}_{16}\text{H}_{13}\text{Br}]$: 284.0201; found: 284.0178 ($[\text{M}-\text{H}_2\text{O}]^+$).

Trimethyl(((1*R,2*S**)-2-((*R**)-1-phenylallyl)cyclohexyl)oxy)silane (89e)**

(See the complete X-ray data at the end of the section)

According to **TP3** cinnamylzinc pivalate (3.00 mL, 0.16 M, 0.48 mmol) was added to a solution of 2-((trimethylsilyl)oxy)cyclohexanone (83 mg, 0.40 mmol) at -78°C and the mixture was stirred 1 h at -78°C . Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a colorless oil (92 mg, 0.32 mmol, 80%, d.r. = 95:5).

M.p. ($^{\circ}\text{C}$): 45.7–74.2.

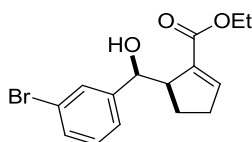
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 7.34–7.14 (m, 5H), 6.47–6.25 (m, 1H), 5.20–4.95 (m, 2H), 3.77–3.56 (m, 1H), 3.56–3.42 (m, 1H), 2.35 (s, 1H), 1.79–1.43 (m, 6H), 1.36–1.25 (m, 1H), 1.17–1.03 (m, 1H), 0.14 (s, 9H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 141.1, 138.2, 129.6, 128.0, 126.4, 116.6, 74.9, 72.7, 55.9, 30.6, 30.6, 22.2, 21.1, 0.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3565, 3426, 3078, 3029, 2948, 2930, 2861, 1630, 1493, 1452, 1446, 1401, 1359, 1346, 1321, 1253, 1150, 1088, 1046, 1032, 1008, 975, 967, 953, 910, 893, 840, 740, 705.

MS (EI, 70 eV): m/z (%) = 187 (29), 171 (100), 155 (2), 141 (7), 129 (15), 117 (34), 103 (8), 91 (15), 73 (31).

HRMS (EI): m/z calc. for $[\text{C}_{15}\text{H}_{18}\text{O}]$: 214.1358; found: 214.1358 ($[\text{M-TMSH}]^+$).

(*R)-Ethyl 5-((*S**)-(3-Bromophenyl)(hydroxy)methyl)cyclopent-1-enecarboxylate (89f)**

According to **TP3** (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc pivalate (5.22 mL, 0.23 M, 1.20 mmol) was added to a solution of 3-bromobenzaldehyde (185 mg, 1.00 mmol) at -78°C and the mixture was stirred 1 h at -78°C . Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1) afforded the title compound as a colorless oil (294 mg, 0.91 mmol, 91%, d.r. = 97:3).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.5–7.5 (m, 1H), 7.4–7.3 (m, 1H), 7.3–7.2 (m, 1H), 7.2–7.1 (m, 1H), 6.9–6.9 (m, 1H), 5.1 (d, J = 3.3 Hz, 1H), 4.3–4.2 (m, 2H), 3.5–3.3 (m, 1H), 3.1 (s, 1H), 2.4–2.2 (m, 2H), 2.0–1.8 (m, 2H), 1.3 (t, J = 7.1 Hz, 3H).

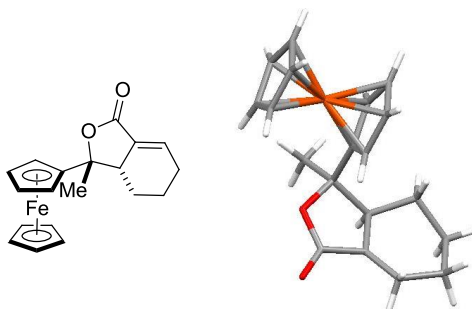
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 166.2, 148.1, 145.5, 136.0, 130.2, 129.7, 129.3, 124.8, 122.4, 73.9, 60.9, 52.0, 32.2, 24.8, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3458, 2979, 2939, 2906, 1690, 1628, 1595, 1569, 1473, 1452, 1447, 1426, 1394, 1372, 1343, 1295, 1253, 1195, 1097, 1069, 1043, 1011, 980, 946, 897, 842, 785, 743, 697, 674.

MS (EI, 70 eV): m/z (%) = 281 (1), 261 (1), 185 (8), 171 (3), 157 (7), 140 (100), 112 (35), 94 (17), 77 (26), 67 (28).

HRMS (EI): m/z calc. for [C₁₅H₁₇⁸¹BrO₃]: 326.0341; found: 326.0508 (M⁺).

(3*R,3*aS**)-3-Methyl-3-ferrocene-3*a*,4,5,6-tetrahydroisobenzofuran-1(3*H*)-one (89g)**



(See the complete X-ray data at the end of the section)

According to **TP3** ((2-(ethoxycarbonyl)cyclohex-2-en-1-yl)zinc pivalate (3.00 mL, 0.40 M, 1.20 mmol) was added to a solution of acetylferrocene (228 mg, 1.00 mmol) at –78 °C and the mixture was stirred 1 h at –78 °C before it was slowly warmed to room temperature overnight. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 10:1) afforded the title compound as a yellow solid (310 mg, 0.92 mmol, 92%, d.r. > 99:1).

M.p. (°C): 171–173.

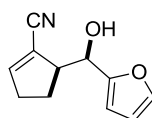
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 6.9–6.7 (m, 1H), 4.2 (s, 5H), 4.2–4.1 (m, 2H), 4.0–3.9 (m, 1H), 3.8–3.7 (m, 1H), 2.9–2.7 (m, 1H), 2.3–2.1 (m, 1H), 2.1–1.9 (m, 1H), 1.9 (s, 3H), 1.8–1.5 (m, 3H), 1.5–1.3 (m, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 170.4, 136.5, 130.8, 91.0, 86.6, 69.2, 68.3, 67.9, 67.2, 64.7, 48.2, 26.8, 25.1, 23.8, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 1749, 1680, 1376, 1254, 1242, 1201, 1154, 1112, 1105, 1025, 998, 946, 932, 919, 899, 871, 862, 850, 830, 812, 791, 738, 715, 679.

MS (EI, 70 eV): m/z (%) = 281 (1), 261 (1), 185 (8), 171 (3), 157 (7), 140 (100), 112 (35), 94 (17), 77 (26), 67 (28).

HRMS (EI): m/z calc. for [C₁₉H₂₀FeO₂]: 336.0813; found: 336.0787 (M⁺).

(S*)-5-((R*)-furan-2-yl(hydroxy)methyl)cyclopent-1-enecarbonitrile (89h)

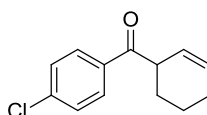
According to **TP3** (2-cyanocyclopent-2-en-1-yl)zinc pivalate (2.70 mL, 0.37 M, 1.00 mmol) was added to a solution of furan-2-carbaldehyde (77 mg, 0.80 mmol) at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$. Purification of the crude product by flash chromatography (silica gel, isohehexane/EtOAc = 5:1) afforded the title compound as a colorless oil (138 mg, 0.73 mmol, 91%, d.r. > 99:1).

^1H -NMR (400 MHz, CDCl_3): δ / ppm = 7.5–7.4 (m, 1H), 6.8–6.7 (m, 1H), 6.4 (dd, J = 3.2, 1.8 Hz, 1H), 6.3 (d, J = 3.3 Hz, 1H), 4.9 (d, J = 4.4 Hz, 1H), 3.5–3.3 (m, 1H), 2.6–2.4 (m, 2H), 2.2–2.0 (m, 3H).
 ^{13}C -NMR (101 MHz, CDCl_3): δ / ppm = 154.6, 151.9, 142.4, 116.1, 115.5, 110.5, 107.4, 68.2, 52.1, 33.1, 24.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2949, 2220, 1732, 1691, 1616, 1504, 1454, 1432, 1375, 1324, 1224, 1149, 1072, 1006, 983, 951, 928, 916, 884, 815, 739.

MS (EI, 70 eV): m/z (%) = 189 (1), 115 (1), 97 (100), 81 (1), 69 (5), 51 (2).

HRMS (EI): m/z calc. for $[\text{C}_{11}\text{H}_{11}\text{NO}_2]$: 189.0790; found: 189.0800 (M^+).

2.14 Regioselective Preparation of β,γ -Unsaturated Ketones of Type 91**(4-Chlorophenyl)(cyclohex-2-en-1-yl)methanone (91a)**

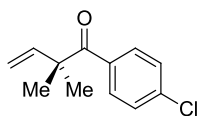
According to **TP4** cyclohex-2-en-1-ylzinc pivalate (3.45 mL, 0.29 M, 1.00 mmol) was added to a solution of 4-chlorobenzoyl chloride (350 mg, 1.50 mmol) at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1.5 h at $-78\text{ }^{\circ}\text{C}$. Purification of the crude product by flash chromatography (silica gel, isohehexane/EtOAc = 100:1) afforded the title compound as a colorless oil (172 mg, 0.78 mmol, 78%).

^1H -NMR (300 MHz, CDCl_3): δ / ppm = 7.96–7.84 (m, 13H), 7.48–7.39 (m, 12H), 5.99–5.87 (m, 7H), 5.76–5.66 (m, 7H), 4.09–3.95 (m, 7H), 2.15–2.03 (m, 13H), 2.02–1.76 (m, 22H), 1.76–1.61 (m, 8H).
 ^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 200.7, 139.4, 134.7, 130.6, 130.1, 129.1, 124.5, 44.1, 25.9, 24.9, 21.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3404, 3029, 2937, 2864, 2837, 1680, 1650, 1587, 1570, 1487, 1449, 1431, 1399, 1348, 1302, 1265, 1248, 1230, 1210, 1175, 1158, 1106, 1090, 1012, 961, 927, 890, 837, 798, 761, 740, 677.

MS (EI, 70 eV): m/z (%) = 220 (M^+ , 17), 185 (3), 141 (100), 111 (82), 75 (34), 50 (11).

HRMS (EI): m/z calc. for $[\text{C}_{13}\text{H}_{14}\text{ClO}^+]$: 221.0728; found: 221.0731 ($[\text{M}+\text{H}]^+$).

1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-one (91b)

According to **TP4** prenylzinc pivalate (3.80 mL, 0.32 M, 1.20 mmol) was added to a solution of 4-chlorobenzoyl chloride (175 mg, 1.00 mmol) at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a colorless oil (194 mg, 0.93 mmol, 93%).

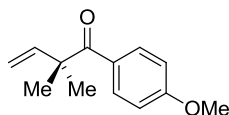
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 7.88–7.80 (m, 2H), 7.38–7.31 (m, 2H), 6.23–6.10 (m, 1H), 5.24 (d, J = 6.8 Hz, 1H), 5.20 (s, 1H), 1.38 (s, 6H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 203.3, 143.8, 138.2, 135.3, 131.0, 128.4, 114.5, 50.3, 26.1.

IR (Diamond-ATR, neat): ν / cm^{-1} = 3539 (vw), 3084 (w), 2975 (m), 2932 (w), 2874 (vw), 1677 (vs), 1633 (m), 1587 (s), 1569 (m), 1486 (m), 1466 (m), 1443 (w), 1412 (m), 1399 (m), 1379 (m), 1363 (m), 1303 (w), 1255 (s), 1220 (m), 1170 (m), 1153 (m), 1090 (vs), 1044 (w), 1012 (s), 970 (vs), 918 (vs), 886 (w), 840 (vs), 759 (vs), 741 (w), 733 (m), 665 (m).

MS (EI, 70 eV): m/z (%) = 175 (95), 127 (15), 105 (100), 91 (7), 77 (42), 69 (93), 51 (14).

HRMS (EI): m/z calc. for $[\text{C}_{12}\text{H}_{13}\text{ClO}]$: 208.0655; found: 208.0629 (M^+).

1-(4-Methoxyphenyl)-4-methylpent-3-en-1-one (91c)

According to **TP4** prenylzinc pivalate (0.28 M, 4.29 mL, 1.20 mmol) was added to a solution of 4-methoxybenzoyl chloride (171 mg, 0.13 mL, 1.00 mmol) at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$ before it was slowly warmed to room temperature overnight. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 40:1) afforded the title compound as a colorless oil (233 mg, 1.14 mmol, 95%).

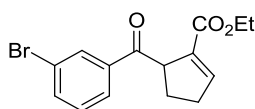
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 7.98–7.93 (m, 2H), 6.88–6.83 (m, 2H), 6.24–6.15 (m, 1H), 5.24–5.16 (m, 2H), 3.83 (s, 3H), 1.39 (s, 6H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 202.5, 162.5, 144.6, 132.1, 129.3, 113.7, 113.2, 55.5, 50.0, 26.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2972, 2934, 2840, 2360, 2340, 2047, 1668, 1633, 1598, 1573, 1508, 1462, 1442, 1417, 1380, 1362, 1307, 1247, 1166, 1150, 1113, 1030, 1012, 996, 971, 917, 839, 820, 787, 767, 736, 702, 670.

MS (EI, 70 eV): m/z (%) = 135 (100), 107 (7), 92 (9), 77 (9).

HRMS (ESI): m/z calc. for $[\text{C}_{13}\text{H}_{17}\text{O}_2]$: 205.1229; found: 205.1213 ($[\text{M}+\text{H}]^+$).

Ethyl 5-(3-Bromobenzoyl)cyclopent-1-enecarboxylate (91d)

According to **TP4** (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc pivalate (5.00 mL, 0.30 M, 1.5 mmol) was added to a solution of 3-bromobenzoyl chloride (296 mg, 1.30 mmol) at -78°C and the mixture was stirred 1 h at -78°C before it was slowly warmed to room temperature overnight. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 15:1) afforded the title compound as a colorless oil (297 mg, 0.92 mmol, 68%).

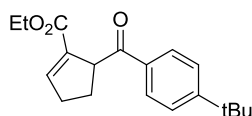
$^1\text{H-NMR}$ (599 MHz, CDCl_3): δ / ppm = 8.13 (s, 1H), 7.93 (d, J = 8.1, 1.4 Hz, 1H), 7.73–7.67 (m, 1H), 7.39–7.33 (m, 1H), 7.06–7.00 (m, 1H), 4.78–4.67 (m, 1H), 4.19–4.06 (m, 2H), 2.76–2.66 (m, 1H), 2.65–2.56 (m, 1H), 2.49–2.40 (m, 1H), 2.08–1.99 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H).

$^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ / ppm = 199.9, 164.1, 146.3, 138.3, 135.8, 131.6, 130.1, 127.1, 122.9, 60.4, 51.4, 32.8, 29.13, 14.1.

IR (Diamond-ATR, neat): ν / cm^{-1} = 2982, 2936, 1721, 1687, 1638, 1566, 1467, 1446, 1421, 1372, 1296, 1280, 1262, 1208, 1174, 1145, 1100, 1070, 1025, 998, 956, 862, 799, 754, 732, 706, 698, 673.

MS (EI, 70 eV): m/z (%) = 322 (1), 278 (30), 183 (100), 155 (21), 139 (2), 93 (4), 76 (10).

HRMS (EI): m/z calc. for $[\text{C}_{13}\text{H}_{10}\text{BrO}_2]^+$: 276.9864; found: 276.9853 ($[\text{M}-\text{OEt}]^+$).

Ethyl 5-(4-(tert-Butyl)benzoyl)cyclopent-1-ene-1-carboxylate (91e)

According to **TP4** (2-cyanocyclohex-2-enyl)zinc pivalate (0.21 M, 4.76 mL, 1.00 mmol) was added to a solution of 4-(tert-butyl)benzoyl chloride (295 mg, 0.29 mL, 1.50 mmol) at -78°C and the mixture was stirred 1 h at -78°C before it was slowly warmed to room temperature overnight. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 40:1) afforded the title compound as a colorless oil (225 mg, 0.75 mmol, 75%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 7.98–7.93 (m, 2H), 7.51–7.46 (m, 2H), 7.03–7.00 (m, 1H), 4.82–4.74 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.74–2.56 (m, 2H), 2.12–1.98 (m, 2H), 1.35 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H).

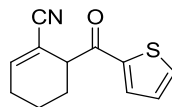
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 200.9, 164.5, 156.9, 146.1, 136.4, 134.0, 128.8, 125.6, 60.4, 51.5, 35.2, 32.9, 31.2, 29.5, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963 (m), 2871 (w), 1712 (vs), 1679 (vs), 1635 (w), 1604 (m), 1566 (w), 1463 (m), 1408 (m), 1394 (w), 1369 (m), 1331 (m), 1269 (vs), 1222 (vs), 1188 (s), 1144 (m), 1096 (vs), 1031 (s), 996 (s), 951 (w), 923 (m), 878 (m), 849 (s), 829 (m), 761 (m), 732 (s), 702 (m).

MS (EI, 70 eV): m/z (%) = 300 (M^+ , 1), 161 (100), 118 (8), 91 (6).

HRMS (EI): m/z calc. for $[C_{19}H_{24}O_3]$: 300.1725; found: 300.1720 (M^+).

6-(Thiophene-2-carbonyl)cyclohex-1-enecarbonitrile (91f)



According to **TP4** (2-Cyanocyclohex-2-enyl)zinc pivalate (4.50 mL, 0.22 M, 1.00 mmol) was added to a solution of thiophene-2-carbonyl chloride (132 mg, 0.90 mmol) at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred 1 h at $-78\text{ }^{\circ}\text{C}$ before it was slowly warmed to room temperature overnight. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1) afforded the title compound as a colorless solid (150 mg, 0.69 mmol, 77%).

M.p. ($^{\circ}\text{C}$): 78.5–79.3.

$^1\text{H-NMR}$ (599 MHz, CDCl_3): δ / ppm = 7.78 (dd, J = 3.8, 1.0 Hz, 1H), 7.71 (dd, J = 4.9, 1.1 Hz, 1H), 7.17 (dd, J = 4.9, 3.9 Hz, 1H), 6.93 (td, J = 4.1, 1.5 Hz, 1H), 4.20–4.06 (m, 1H), 2.38–2.18 (m, 2H), 2.14–1.94 (m, 2H), 1.84–1.64 (m, 2H).

$^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ / ppm = 191.3, 148.8, 142.6, 134.9, 132.8, 128.5, 118.7, 110.9, 45.7, 26.8, 25.7, 18.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3113, 3092, 2934, 2862, 2215, 1645, 1518, 1449, 1412, 1353, 1336, 1317, 1288, 1248, 1213, 1151, 1127, 1078, 1046, 995, 952, 941, 926, 888, 858, 828, 794, 762, 736, 665.

MS (EI, 70 eV): m/z (%) = 217 (5), 111 (100), 83 (10).

HRMS (EI): m/z calc. for $[C_{12}H_{11}ONS]$: 217.0561; found: 217.0568 (M^+).

2.15 Crystallographic Data

Trimethyl(((1*R*,2*S*)-2-((*R*)-1-phenylallyl)cyclohexyl)oxy)silane (**89e**)

CCDC 1061748 contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

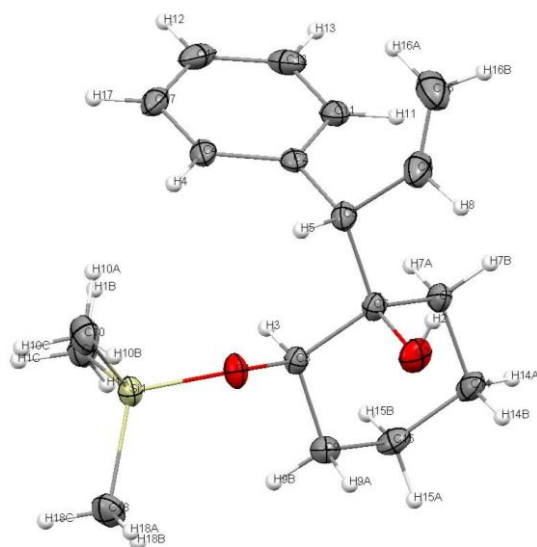


Figure 7: ORTEP representation of **89e** with the thermal ellipsoids set at 30% probability level.

Crystal data:

Chemical formula	C ₁₈ H ₂₉ O ₂ Si
<i>M_r</i>	304.49
Crystal system, space group	Triclinic, <i>P</i> 1
Temperature (K)	173
<i>a</i> , <i>b</i> , <i>c</i> (Å)	9.4526 (5), 9.9546 (6), 10.1993 (6)
α, β, γ (°)	109.366 (5), 93.388 (5), 104.106 (5)
<i>V</i> (Å ³)	867.79 (9)
<i>Z</i>	2
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.14
Crystal size (mm)	0.42 × 0.27 × 0.17
Data collection	
Absorption correction	Multi-scan
<i>T_{min}</i> , <i>T_{max}</i>	0.984, 0.992
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	4566, 3130, 2645
<i>R_{int}</i>	0.025
(sin θ/λ) _{max} (Å ⁻¹)	0.602
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.056, 0.159, 1.08
No. of reflections	3130
No. of parameters	194
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ _{max} , Δρ _{min} (e Å ⁻³)	1.14, -0.44

(3*R,3*aS**)-3-Methyl-3-ferrocene-3*a*,4,5,6-tetrahydroisobenzofuran-1(3*H*)-one (89g)**

CCDC 1061747 contains the supplementary crystallographic data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

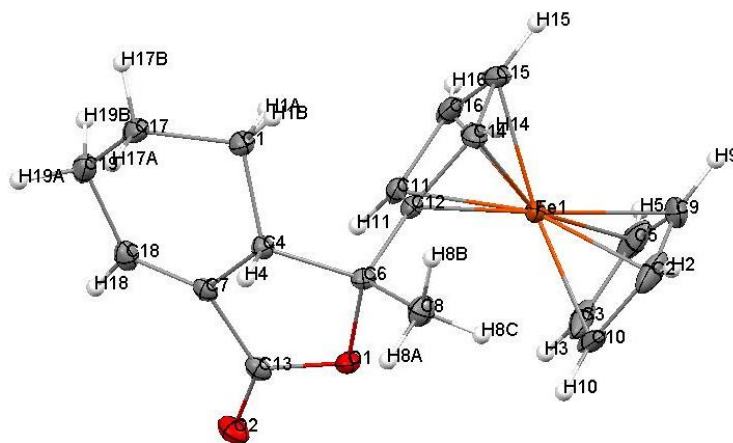


Figure 8: ORTEP representation of **89g** with the thermal ellipsoids set at 30% probability level.

Crystal data:

Chemical formula	C ₁₉ H ₂₀ FeO ₂
<i>M_r</i>	336.20
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁ / <i>n</i>
Temperature (K)	173
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.0951 (2), 13.0246 (5), 19.2405 (7)
β (°)	93.758 (1)
<i>V</i> (Å ³)	1524.15 (9)
<i>Z</i>	4
Radiation type	Mo <i>K</i> α
μ (mm ⁻¹)	0.99
Crystal size (mm)	0.12 × 0.08 × 0.06
Data collection	
Absorption correction	Multi-scan
<i>T</i> _{min} , <i>T</i> _{max}	0.890, 0.943
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	26281, 3131, 2736
<i>R</i> _{int}	0.028
(sin θ/λ) _{max} (Å ⁻¹)	0.626
Refinement	
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.028, 0.094, 1.19
No. of reflections	3131
No. of parameters	200
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ _{max} , Δρ _{min} (e Å ⁻³)	0.41, -0.30

3 Preparation and Application of Solid, Salt Stabilized Amide Enolates

3.1 Typical Procedures

TP1: Typical Procedure for the Preparation of the Solid Morpholine Amide Zinc Pivalates

A dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the morpholine amide (10.0 mmol) and THF to give a 1 M solution. $\text{TMPZnCl}\cdot\text{LiCl}$ (1.31 M in THF, 13.0 mmol) was added. After stirring the reaction mixture for 2 h at room temperature $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) was added and the mixture was stirred 15 min until a clear solution was formed. The solvent was removed *in vacuo* and the dried solid morpholine amide zinc pivalate was titrated using iodine (see Chapter 2.1) in order to determine the yield.

TP2: Typical Procedure for Negishi Couplings using Morpholine Amide Zinc Pivalates

A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the solid morpholine amide zinc pivalate (0.50 mmol), $\text{Pd}(\text{dba})_2$ (2 mol%), DavePhos (4 mol%) and THF to give a 0.5 M solution respective to the morpholine amide zinc pivalate. The electrophile (0.38 mmol) was added and the suspension was stirred at 40 °C for 4 h. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution (30 mL) and dried over MgSO_4 . After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the Negishi coupling product.

TP3: Typical Procedure for Aldol type reactions using Morpholine Amide Zinc Pivalates

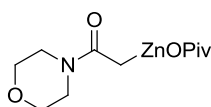
A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the solid morpholine amide zinc pivalate (0.50 mmol) and THF to give a 0.5 M solution respective to the morpholine amide zinc pivalate. The solution was cooled to 0 °C and the carbonyl compound (0.40 mmol) was added. The reaction mixture was stirred for 3 h at 0 °C before quenching it with sat. aq. NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution (30 mL) and dried over MgSO_4 . After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the aldol product.

TP4: Typical Procedure for Allylation reactions using Morpholine Amide Zinc Pivalates

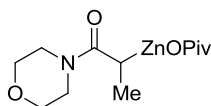
A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with the solid morpholine amide zinc pivalate (0.30 mmol) and THF to give a 0.3 M solution respective to the morpholine amide zinc pivalate. The solution was cooled to –30 °C and 20 mol% $\text{CuCN}\cdot 2\text{LiCl}$ was added. The allylic electrophile (0.24 mmol) was added and the solution was stirred for 4 h at –30 °C. A mixture of sat. aq. NH_4Cl and aq. NH_3 (25%) solutions (8:1, 10 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. NaCl solution 30 mL and dried over MgSO_4 . After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography furnished the allylation product.

TP5: Typical Procedure for the Substitution of the Morpholine Moiety using Grignard Reagents

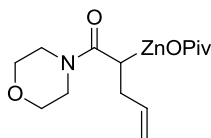
A dry and argon-flushed flask equipped with a magnetic stirring bar and a septum was charged with $\text{LaCl}_3 \cdot 2\text{LiCl}$ (0.50 M in THF, 0.70 mmol), the Grignard reagent (1.64 M in THF, 0.70 mmol) and cooled to 0 °C. The morpholine amide (0.48 mmol) dissolved in THF (1 mL) was added and the resulting dark solution was stirred for 4.5 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl solution (20 mL) and water (40 mL). The mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with sat. aq. NH_4Cl solution (50 mL) and dried over MgSO_4 . After filtration, the solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded the substituted product.

3.2 Preparation of the Solid Morpholine Amide Zinc Pivalates**(2-Morpholino-2-oxoethyl)zinc pivalate (93a)**

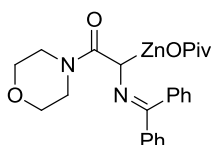
According to **TP1** $\text{TMPZnCl} \cdot \text{LiCl}$ (1.31 M in THF, 15.6 mL, 12.0 mmol) was added to a solution of 1-morpholinoethan-1-one **92a** (1.29 g, 10.0 mmol) in THF (10 mL). The mixture was stirred for 1.5 h at room temperature. Addition of $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and removal of the solvent furnished the title compound as a light yellow solid. Determination of the content of active zinc species by titration with iodine indicated a concentration of 0.80 mmol g^{-1} corresponding a yield of 78%.

(1-Morpholino-1-oxopropan-2-yl)zinc pivalate (93b)

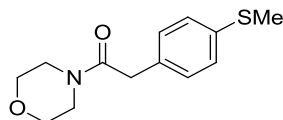
According to **TP1** $\text{TMPZnCl} \cdot \text{LiCl}$ (1.31 M in THF, 15.6 mL, 12.0 mmol) was added to a solution of 1-morpholinopropan-1-one **92b** (1.43 g, 10.0 mmol) in THF (10 mL). The mixture was stirred for 2 h at room temperature. Addition of $\text{Mg}(\text{OPiv})_2$ (2.72 g, 12.0 mmol) and removal of the solvent furnished the title compound as a yellow solid. Determination of the content of active zinc species by titration with iodine indicated a concentration of 0.90 mmol g^{-1} corresponding a yield of 86%.

(1-Morpholino-1-oxopent-4-en-2-yl)zinc pivalate (93c)

According to **TP1** TMPZnCl·LiCl (1.31 M in THF, 15.6 mL, 12.0 mmol) was added to a solution of 1-morpholinopent-4-en-1-one **92c** (1.68 g, 10.0 mmol) in THF (10 mL). The mixture was stirred for 2 h at room temperature. Addition of Mg(OPiv)₂ (2.72 g, 12.0 mmol) and removal of the solvent furnished the title compound as a yellow solid. Determination of the content of active zinc species by titration with iodine indicated a concentration of 0.64 mmol g⁻¹ corresponding a yield of 65%.

(1-((diphenylmethylene)amino)-2-morpholino-2-oxoethyl)zinc pivalate (93d)

According to **TP1** TMPZnCl·LiCl (1.31 M in THF, 15.6 mL, 12.0 mmol) was added to a solution of 2-((diphenylmethylene)amino)-1-morpholinoethanone **92d** (3.08 g, 10.0 mmol) in THF (10 mL). The mixture was stirred for 2 h at room temperature. Addition of Mg(OPiv)₂ (2.72 g, 12.0 mmol) and removal of the solvent furnished the title compound as a yellow solid. Determination of the content of active zinc species by titration with iodine indicated a concentration of 0.72 mmol g⁻¹ corresponding a yield of 83%.

3.3 Preparation of Cross-Coupling, Allylation and Carbonyl Addition Products**2-(4-(Methylthio)phenyl)-1-morpholinoethanone (94a)**

According to **TP2** 4-bromothioanisole **3f** (906 mg, 4.46 mmol) was added to a solution of (2-morpholino-2-oxoethyl)zinc pivalate **93a** (0.65 mmol g⁻¹, 8.52 g, 5.57 mmol), Pd(dba)₂ (2 mol%, 63.3 mg) and DavePhos (4 mol%, 87.7 mg) in THF (19 mL) and the resulting dark mixture was stirred at room temperature over night. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:2) afforded the title compound as a yellow oil (1.11 g, 4.42 mmol, 99%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.23–7.20 (m, 2H), 7.17–7.14 (m, 2H), 3.68 (s, 2H), 3.64 (m, 4H), 3.52–3.48 (m, 2H), 3.42 (m, 2H), 2.47 (s, 3H).

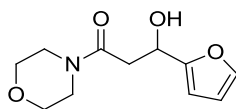
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 169.6, 137.1, 131.7, 129.2, 127.2, 66.9, 66.6, 46.6, 42.3, 40.4, 16.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2962 (w), 2918 (w), 2853 (w), 1640 (vs), 1494 (m), 1456 (m), 1433 (m), 1406 (w), 1361 (w), 1328 (w), 1300 (w), 1271 (m), 1251 (w), 1230 (m), 1195 (w), 1159 (w), 1114 (s), 1093 (w), 1068 (w), 1036 (w), 1017 (w), 966 (w), 852 (w), 806 (w), 775 (w).

MS (EI, 70 eV): m/z (%) = 251 (M⁺, 100), 164 (7), 137 (78), 114 (45), 70 (21).

HRMS (EI): m/z calc. for [C₁₃H₁₇NO₂³²S]: 251.0980; found: 251.0980 (M⁺).

3-(Furan-2-yl)-3-hydroxy-1-morpholinopropan-1-one (95a)



According to **TP3** furfural **88c** (37.0 mg, 0.39 mmol) was added to a solution of (2-morpholino-2-oxoethyl)zinc pivalate **93a** (0.65 mmol g⁻¹, 736 mg, 0.48 mmol) in THF (1 mL) and the resulting dark mixture was stirred for 4 h at 0 °C. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:2) afforded the title compound as a colorless oil (87 mg, 0.39 mmol, 99%).

¹H-NMR (800 MHz, CDCl₃): δ / ppm = 7.13–7.12 (m, 1H), 6.36 (d, J = 3.1 Hz, 1H), 6.14 (dd, J = 3.3, 1.8 Hz, 1H), 5.29 (dt, J = 9.4, 3.2 Hz, 1H), 5.01 (d, J = 3.7 Hz, 1H), 3.33 (m, 1H), 3.21 (m, 1H), 3.14 (m, 2H), 2.96 (m, 2H), 2.44 (dd, J = 16.3, 9.3 Hz, 1H), 2.40 (m, 2H), 2.27 (dd, J = 16.3, 2.8 Hz, 1H).

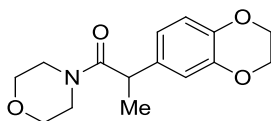
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 170.2, 156.9, 141.6, 110.8, 106.3, 66.5, 66.2, 65.2, 45.2, 41.8, 38.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3395 (w), 3117 (w), 2964 (w), 2918 (w), 2859 (w), 2762 (vw), 1614 (vs), 1504 (w), 1463 (m), 1439 (s), 1362 (w), 1343 (w), 1330 (w), 1302 (m), 1271 (m), 1228 (m), 1172 (w), 1145 (m), 1111 (vs), 1066 (s), 1039 (m), 1008 (s), 965 (m), 944 (w), 914 (w), 882 (w), 852 (m), 815 (w), 742 (m).

MS (EI, 70 eV): m/z (%) = 225 (M⁺, 100), 197 (13), 179 (2), 156 (9), 129 (15), 114 (19), 97 (54), 70 (10), 56 (16).

HRMS (EI): m/z calc. for [C₁₁H₁₅NO₄]: 225.1001; found: 225.1002 (M⁺).

2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-morpholinopropan-1-one (94b)



According to **TP2** 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine **85k** (86.2mg, 0.40 mmol) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.79 mmol g⁻¹, 633 mg, 0.50 mmol) Pd(dba)₂ (2 mol%, 5.76 mg) and DavePhos (4 mol%, 7.89 mg) in THF (0.5 mL) and the resulting dark

mixture was stirred at room temperature over night. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:1) afforded the title compound as a yellow oil (117 mg, 0.42 mmol, 99%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 6.80 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 2.1 Hz, 1H), 6.68 (dd, J = 8.3, 2.2 Hz, 1H), 4.24 (m, 4H), 3.73 (q, J = 6.9 Hz, 1H), 3.70–3.17 (m, 8H), 1.41 (d, J = 6.8 Hz, 3H).

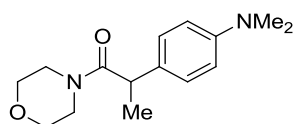
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 172.4, 143.9, 142.6, 135.2, 120.2, 117.8, 116.1, 66.9, 66.6, 64.5, 64.4, 46.2, 42.6, 42.5, 20.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2970 (w), 2928 (w), 2896 (w), 2856 (w), 1732 (vw), 1638 (vs), 1588 (m), 1504 (vs), 1456 (s), 1430 (s), 1362 (w), 1284 (vs), 1262 (s), 1248 (s), 1224 (s), 1198 (m), 1148 (w), 1114 (vs), 1092 (w), 1066 (vs), 1030 (s), 1010 (m), 948 (m), 936 (w), 912 (m), 900 (m), 884 (s), 846 (m), 818 (m), 792 (m), 768 (w), 738 (m), 724 (w), 698 (w).

MS (EI, 70 eV): m/z (%) = 277 (M⁺, 20), 163 (100), 119 (3), 91 (13), 65 (5).

HRMS (EI): m/z calc. for [C₁₅H₁₉NO₄]: 277.1314; found: 277.1309 (M⁺).

2-(4-(Dimethylamino)phenyl)-1-morpholinopropan-1-one (94c)



According to **TP2** 4-bromo-*N,N*-dimethylaniline **85i** (90.6 mg, 0.45 mmol) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.79 mmol g⁻¹, 715 mg, 0.57 mmol), Pd(dba)₂ (2 mol%, 6.50 mg) and DavePhos (4 mol%, 8.67 mg) in THF (0.6 mL) and the resulting dark mixture was stirred at 40 °C for 4 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1 + 4% NEt₃ → 3:1 + 4% NEt₃) afforded the title compound as a yellow oil (115 mg, 0.44 mmol, 97%).

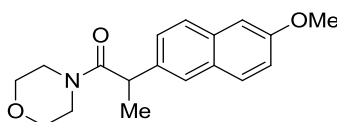
¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.13–7.03 (m, 2H), 6.72–6.63 (m, 2H), 3.81–3.71 (m, 2H), 3.69–3.61 (m, 1H), 3.57–3.44 (m, 3H), 3.44–3.30 (m, 2H), 3.14 (m, 1H), 2.92 (s, 6H), 1.41 (d, J = 6.8 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 172.9, 149.5, 129.7, 127.9, 113.1, 66.9, 66.5, 46.1, 42.5, 42.3, 40.8, 20.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2966 (w), 2926 (w), 2894 (w), 2854 (m), 2802 (w), 1640 (vs), 1614 (s), 1564 (w), 1520 (vs), 1480 (w), 1454 (s), 1444 (s), 1428 (s), 1348 (m), 1298 (m), 1268 (m), 1230 (s), 1198 (s), 1182 (m), 1164 (m), 1112 (vs), 1066 (m), 1030 (s), 1010 (m), 998 (m), 946 (m), 906 (w), 846 (m), 820 (s), 780 (m), 742 (m), 730 (m), 700 (w), 662 (m).

MS (EI, 70 eV): m/z (%) = 262 (M⁺, 17), 148 (100), 132 (5), 118 (2), 104 (2).

HRMS (EI): m/z calc. for [C₁₅H₂₂N₂O₂]: 262.1681; found: 262.1678 (M⁺).

2-(6-Methoxynaphthalen-2-yl)-1-morpholinopropan-1-one (94d)

According to **TP2** 2-bromo-6-methoxynaphthalene **85m** (61.2 mg, 0.27 mmol) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.73 mmol g⁻¹, 455 mg, 0.33 mmol), Pd(dba)₂ (2 mol%, 3.85 mg) and DavePhos (4 mol%, 5.24 mg) in THF (0.7 mL) and the resulting dark mixture was stirred at 40 °C for 4 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a colorless oil (80.0 mg, 0.27 mmol, 99%).

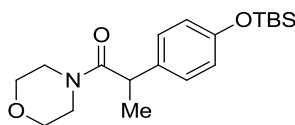
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.71 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 3.97 (q, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.79 (m, 1H), 3.73–3.63 (m, 1H), 3.54 (m, 2H), 3.50–3.39 (m, 2H), 3.34 (m, 1H), 3.08 (m, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 172.4, 157.8, 137.1, 133.6, 129.3, 129.2, 127.8, 126.1, 125.6, 119.3, 105.8, 66.9, 66.5, 55.5, 46.2, 43.4, 42.6, 20.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2966 (w), 2928 (w), 2900 (w), 2854 (w), 1640 (vs), 1606 (s), 1504 (w), 1484 (m), 1458 (m), 1430 (s), 1392 (m), 1366 (w), 1300 (w), 1266 (s), 1228 (s), 1212 (s), 1172 (m), 1116 (s), 1092 (w), 1068 (w), 1030 (s), 944 (w), 924 (w), 894 (w), 854 (m), 814 (w), 728 (w), 676 (w).

MS (EI, 70 eV): *m/z* (%) = 299 (M⁺, 25), 185 (100), 170 (10), 155 (6), 141 (9), 115 (5).

HRMS (EI): *m/z* calc. for [C₁₈H₂₁NO₃]: 299.1521; found: 299.1517 (M⁺).

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-morpholinopropan-1-one (94e)

According to **TP2** *tert*-butyl(4-iodophenoxy)dimethylsilane **96a** (130 mg, 0.39 mmol) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.73 mmol g⁻¹, 662 mg, 0.49 mmol), Pd(dba)₂ (2 mol%, 5.58 mg) and DavePhos (4 mol%, 7.63 mg) in THF (0.5 mL) and the resulting dark mixture was stirred at 25 °C for 5.5 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 3:1) afforded the title compound as a slightly brown solid (122 mg, 0.35 mmol, 90%).

M.p. (°C): 67.5–71.0.

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.12–7.03 (m, 2H), 6.82–6.74 (m, 2H), 3.77 (m, 2H), 3.66 (m, 1H), 3.50 (m, 3H), 3.34 (m, 2H), 3.10 (m, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 9H), 0.18 (s, 6H).

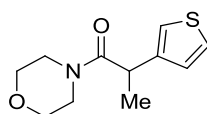
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 172.6, 154.6, 134.7, 128.3, 120.7, 66.9, 66.5, 46.2, 42.6, 42.5, 25.8, 20.8, 18.4, -4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3028 (vw), 2958 (m), 2930 (m), 2896 (w), 2858 (m), 1732 (vw), 1646 (s), 1608 (m), 1580 (vw), 1558 (vw), 1508 (s), 1472 (m), 1460 (m), 1430 (m), 1390 (w), 1362 (w), 1298 (w), 1252 (vs), 1230 (s), 1172 (m), 1114 (s), 1090 (w), 1068 (m), 1030 (m), 1014 (w), 1006 (w), 938 (m), 912 (vs), 838 (vs), 812 (s), 780 (s), 734 (w), 724 (w), 680 (m).

MS (EI, 70 eV): m/z (%) = 349 (M⁺, 5), 235 (100), 177 (5), 163 (5), 144 (8), 73 (4).

HRMS (EI): m/z calc. for [C₁₉H₃₁NO₃²⁸Si]: 349.2073; found: 349.2067 (M⁺).

1-Morpholino-2-(thiophen-3-yl)propan-1-one (94f)



According to **TP2** 3-bromothiophene **85h** (192 mg, 1.18 mmol) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.79 mmol g⁻¹, 1.85 g, 1.47 mmol), Pd(dba)₂ (2 mol%, 16.9 mg) and DavePhos (4 mol%, 23.1 mg) in THF (1.5 mL) and the resulting dark mixture was stirred at 40 °C for 3 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 2:1) afforded the title compound as a yellow oil (215 mg, 0.95 mmol, 81%).

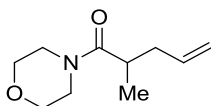
¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.29 (dd, J = 5.0, 3.0 Hz, 1H), 7.05–7.03 (m, 1H), 6.99 (dd, J = 5.0, 1.3 Hz, 1H), 4.00 (q, J = 6.9 Hz, 1H), 3.78 (m, 1H), 3.71–3.64 (m, 1H), 3.58–3.50 (m, 3H), 3.44–3.36 (m, 2H), 3.27–3.21 (m, 1H), 1.45 (d, J = 6.9 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 172.2, 142.0, 126.9, 126.5, 120.8, 66.9, 66.6, 46.3, 42.6, 38.4, 19.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3094 (vw), 2970 (w), 2930 (w), 2898 (w), 2856 (w), 1644 (vs), 1530 (vw), 1458 (m), 1432 (m), 1386 (w), 1362 (w), 1332 (vw), 1300 (w), 1270 (w), 1232 (m), 1194 (w), 1152 (vw), 1114 (s), 1090 (w), 1068 (w), 1030 (m), 1014 (w), 946 (w), 918 (vw), 902 (vw), 862 (w), 846 (w), 830 (vw), 800 (w), 774 (w), 748 (vw), 694 (vw), 662 (w).

MS (EI, 70 eV): m/z (%) = 225 (M⁺, 71), 210 (22), 192 (4), 167 (5), 138 (6), 111 (100), 85 (7), 70 (30), 56 (8).

HRMS (EI): m/z calc. for [C₁₁H₁₅NO₂³²S]: 225.0823; found: 225.0821 (M⁺).

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-morpholinopropan-1-one (98a)


According to **TP4** CuCN·2LiCl (10 mol%, 1.00 M in THF, 0.03 mL) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.73 mmol g⁻¹, 434 mg, 0.32 mmol) in THF (1 mL) at 0 °C. Allyl bromide **97a** (30.8 mg, 0.25 mmol) was added and the resulting orange solution was stirred at 0 °C for 2.5 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:1) afforded the title compound as a colorless oil (59.0 mg, 0.32 mmol, 90%).

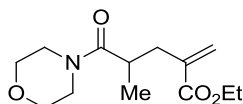
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.76 (dddd, *J* = 16.9, 10.1, 7.6, 6.5 Hz, 1H), 5.07–4.96 (m, 2H), 3.48–2.72 (m, 8H), 2.53 (m, 1H), 2.27 (m, 1H), 2.08 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 173.5, 136.8, 116.5, 67.0, 66.8, 45.8, 42.3, 38.6, 35.2, 17.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3480 (w), 3076 (w), 2970 (w), 2856 (m), 1636 (vs), 1462 (m), 1432 (s), 1362 (w), 1326 (w), 1300 (w), 1268 (m), 1234 (s), 1218 (m), 1156 (w), 1114 (vs), 1068 (m), 1028 (s), 996 (m), 956 (w), 914 (m), 878 (w), 844 (m), 748 (w), 724 (w).

MS (EI, 70 eV): *m/z* (%) = 183 (M⁺, 34), 168 (33), 154 (18), 140 (25), 114 (47), 100 (10), 86 (51), 69 (100), 55 (36).

HRMS (EI): *m/z* calc. for [C₁₀H₁₇NO₂]: 183.1259; found: 183.1246 (M⁺).

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-morpholinopropan-1-one (98b)


According to **TP4** CuCN·2LiCl (10 mol%, 1.00 M in THF, 0.03 mL) was added to a solution of (1-morpholino-1-oxopropan-2-yl)zinc pivalate **93b** (0.73 mmol g⁻¹, 394 mg, 0.29 mmol) in THF (1 mL) at –20 °C. Ethyl 2-(bromomethyl)acrylate **97b** (44.5 mg, 0.23 mmol) was added and the resulting orange solution was stirred at –20 °C for 2 h. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colorless oil (57.0 mg, 0.22 mmol, 97%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 6.15 (d, *J* = 1.8 Hz, 1H), 5.41 (m, 1H), 3.95 (m, 2H), 3.59–2.97 (m, 8H), 2.97–2.81 (m, 2H), 2.40 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

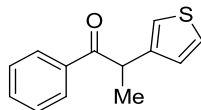
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 173.6, 166.9, 138.7, 127.3, 67.0, 66.9, 60.6, 45.9, 42.4, 37.5, 34.1, 17.2, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2972 (w), 2930 (w), 2856 (w), 1710 (s), 1640 (s), 1462 (m), 1434 (s), 1370 (m), 1326 (m), 1302 (m), 1280 (m), 1268 (m), 1236 (s), 1210 (m), 1192 (m), 1156 (s), 1114 (vs), 1068 (m), 1026 (s), 948 (m), 890 (w), 846 (w), 818 (w), 682 (w).

MS (EI, 70 eV): *m/z* (%) = 255 (M⁺, 23), 241 (4), 227 (14), 210 (46), 182 (100), 168 (56), 141 (56), 127 (4), 113 (90), 95 (45), 81 (16), 67 (23), 53 (11).

HRMS (EI): m/z calc. for $[C_{13}H_{21}NO_4]$: 255.1471; found: 255.1462 (M^+).

1-Phenyl-2-(thiophen-3-yl)propan-1-one (99)



According to **TP5** PhMgCl·LiCl (1.64 M in THF, 0.43 mL, 0.71 mmol) was added to a solution of $LaCl_3 \cdot 2LiCl$ (0.50 M in THF, 1.43 mL, 0.71 mmol) at 0 °C. 1-Morpholino-2-(thiophen-3-yl)propan-1-one **4c** (107mg, 0.48 mmol) dissolved in THF (1 mL) was added and the resulting dark solution was stirred for 4.5 h at 0 °C. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (99 mg, 0.46 mmol, 96%).

1H -NMR (400 MHz, C_6D_6): δ / ppm = 7.90–7.85 (m, 2H), 7.07–6.96 (m, 3H), 6.81 (dd, J = 5.0, 1.4 Hz, 1H), 6.76 (dd, J = 5.0, 2.9 Hz, 1H), 6.71 (dd, J = 2.9, 1.2 Hz, 1H), 4.38 (q, J = 6.8 Hz, 1H), 1.43 (d, J = 6.8 Hz, 3H).

^{13}C -NMR (100 MHz, C_6D_6): δ / ppm = 199.0, 142.1, 137.0, 132.6, 129.0, 128.6, 127.3, 126.2, 121.5, 43.1, 19.1.

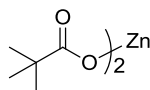
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3102 (w), 3062 (w), 2976 (w), 2932 (w), 2874 (w), 1680 (vs), 1648 (w), 1596 (m), 1580 (w), 1528 (w), 1448 (m), 1410 (w), 1372 (w), 1334 (m), 1306 (w), 1272 (w), 1224 (s), 1182 (m), 1154 (w), 1080 (w), 1002 (w), 958 (s), 930 (w), 910 (w), 862 (m), 830 (w), 782 (m), 754 (m), 722 (s), 688 (m), 658 (m).

MS (EI, 70 eV): m/z (%) = 216 (M^+ , 30), 105 (100), 77 (34), 51 (7).

HRMS (EI): m/z calc. for $[C_{13}H_{12}O_{32}S]$: 216.0609; found: 216.0603 (M^+).

4 Scalable Preparation of Functionalized (Hetero-)Arylzinc Pivalates

4.1 Zinc Pivalate



A flame-dried and argon-flushed 500 mL three-necked round-bottom flask, equipped with a 5 × 2-cm Teflon-coated magnetic stirring bar, a rubber septum an argon line inlet and a pressure equalizer, was charged with dry THF (60 mL).¹¹³ The apparatus was maintained under an atmosphere of argon during the course of the reaction. Pivalic acid (**101**, 10.2 g, 11.3 mL, 100 mmol)¹¹⁴ was added to form a colorless

¹¹³ Pivalic acid (99%) was obtained from Acros Organics and warmed to 60 °C ca. 1 h prior to the addition. The molten pivalic acid can be easily added by quickly handling via syringe.

¹¹⁴ THF was continuously refluxed and freshly distilled from sodium benzophenone.

solution. The mixture was cooled in an ice bath and stirred at 0 °C. In a second flame dried and argon-flushed 250 mL Schlenk flask, equipped with a 3.5 × 1.5-cm Teflon-coated magnetic stirring bar and a rubber septum, neat diethylzinc (6.50 g, 5.40 mL, 52.5 mmol) was added to 60 mL dry THF.^{115,116} The solution should be prepared shortly before the addition (<15 min), as Et₂Zn reacts slowly with THF. The freshly prepared Et₂Zn solution was cannulated to the three-necked round-bottom flask at 0 °C over a period of 15 min under vigorous stirring (Figure 9).¹¹⁷

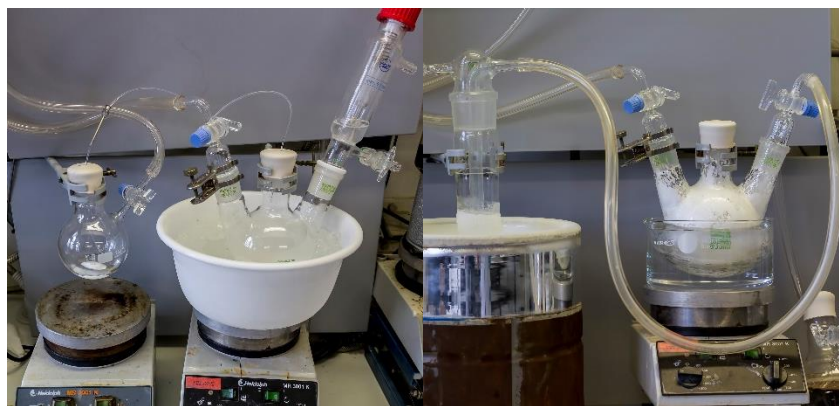


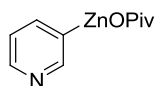
Figure 9: Cannulation of the diethylzinc solution to the reaction flask and evaporation of the solvent using a liquid nitrogen cold trap.

The ice-bath was removed and stirring continued at 25 °C for two additional hours at which point bubbling was ceased (a thick slurry was formed). Then, the pressure equalizer was replaced with a glass cap and the solvent was removed *in vacuo* using a vacuum line and a liquid nitrogen cold trap (1000 mL) (Figure 9). The flask was warmed in a 20 °C water bath and the solid residue was dried for at least 4 h longer.¹¹⁸ Zn(OPiv)₂ (**100**) was received in quantitative yield, as a puffy amorphous white solid.¹¹⁹

¹H NMR (800 MHz, DMSO-*d*₆): δ/ppm = 1.08 (s, 9H)

¹³C NMR (201 MHz, DMSO-*d*₆): δ/ppm = 183.9, 37.7, 28.2.

4.2 Pyridin-3-ylzinc Pivalate



A dry and argon flushed 1 L Schlenk-flask equipped with a 5 × 2-cm Teflon-coated magnetic stirring bar and a septum was filled with argon and then weighed. The flask was charged with 3-bromopyridine

¹¹⁵ Care should be taken for the addition of Et₂Zn to avoid exposure of the pyrophoric reagent to ambient atmosphere.

¹¹⁶ Diethylzinc was obtained in a steel cylinder from Chemtura Corporation and used as received.

¹¹⁷ A BOLA tube (0.8 × 1.6 mm, ca. 20 cm length) was used. The mixture was stirred at 900 rpm throughout the reaction.

¹¹⁸ The flask is connected to high vacuum (0.1 mmHg) with liquid nitrogen cold trap. Vigorous stirring (800 rpm) was maintained to keep the solid from forming solvent cages.

¹¹⁹ Zinc pivalate should be stored under argon, but can be weighed on air.

(6.32 g, 40.0 mmol)¹²⁰ and dry THF (50 mL). The solution was cooled in an ice bath and stirred for at least 5 min at 0 °C before *i*PrMgCl·LiCl (34.9 mL, 1.26 M, 44.0 mmol)¹²¹ was added with a syringe pump over the period of 30 min. The ice bath was removed and the solution is stirred for 3 h at 25 °C during which time it gradually turns from yellow to dark red.¹²² Upon completion of the reaction, solid Zn(OPiv)₂ (**100**, 12.3 g, 46.0 mmol) was added in one portion under argon counterflow. A slight exotherm was noted. The mixture was stirred at r.t. for 30 min during which a clear dark red solution was formed. The solvent was removed using a vacuum line (0.1 mmHg) and a liquid nitrogen cold trap and the solid residue was dried for at least 2 h longer during which a voluminous yellow foam was formed (Figure 10).¹²³ The foam was crushed with a spatula under argon counterflow to form a yellow fine powder. The powder was dried under high vacuum for further 2 h. Pyridine-3-ylzinc pivalate (**103**, 30.0 g, 1.19 mmol g⁻¹, 35.6 mmol, 89%) is stored under an inert atmosphere in the dark for long-term storage and can be weighed on air without significant loss of activity.

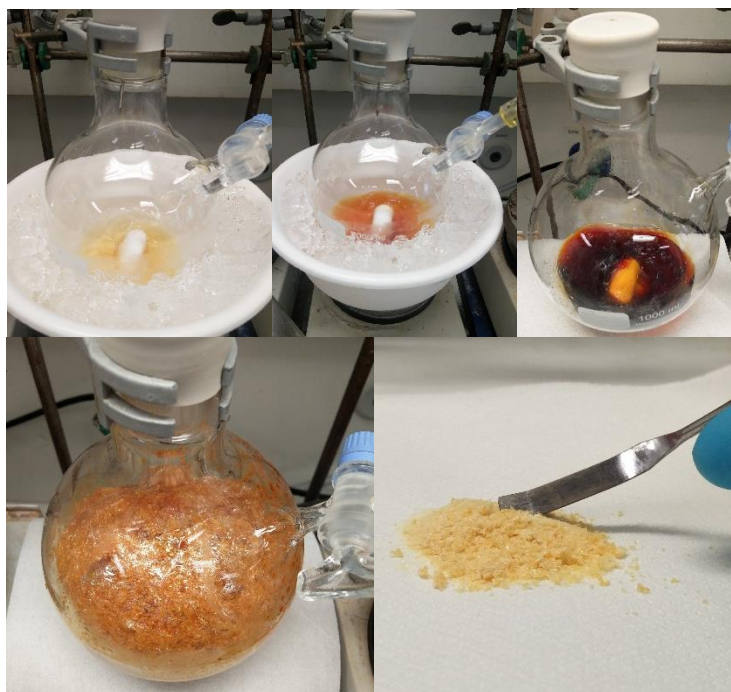


Figure 10: The color of the reaction mixture turns from yellow to dark red. Photographs of the solid foam and powder.

After the drying process was complete the argon flushed flask was weighed to determine the weight of the formed powder. To determine the actual content in zinc species and the yield of the reaction, a small

¹²⁰ 3-Bromopyridine (99%) was purchased from Apollo Scientific and used as received.

¹²¹ A solution of *i*PrMgCl·LiCl in THF was obtained from Rockwood Lithium and titrated against Iodine prior to use. For the titration accurately weighted aliquots (e.g. 221 mg) I₂ were placed in a dry and argon flushed 20 mL Schlenk flask with a septum and dissolved in ca. 2 mL dry THF. To the solution thus formed, was added the *i*PrMgCl·LiCl solution using a 1 mL NORM-JECT syringe from Henke Sass Wolf until the complete disappearance of the dark brown color of iodine (0.69 mL equals a concentration of 1.26 M).

¹²² The progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with I₂.

¹²³ The flask was warmed in a 20 °C water bath to accelerate the solvent evaporation.

aliquot of the powder (ca. 1 g, see Figure 3: A) was titrated using a 1 M solution of iodine in THF¹²⁴ with a color change from red (B) to bright yellow (C) until the persisting brown color of the iodine (D) indicates the completion of the titration.¹²⁵

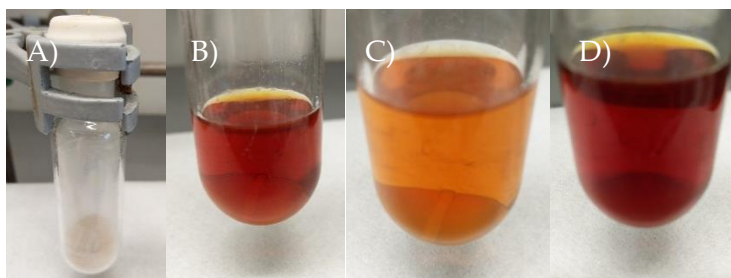
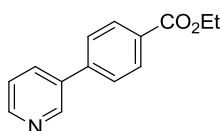


Figure 11: Titration of the organozinc reagent.

4.3 Ethyl 4-(Pyridin-3-yl)benzoate



In a dry and argon-flushed 250 mL Schlenk-flask, equipped with a 5 × 2-cm Teflon-coated magnetic stirring bar and a septum, the solid pyridine-3-ylzinc pivalate (23.4 g, 30.4 mmol, 1.30 mmol g⁻¹) was dissolved in dry THF (60 mL). Ethyl 4-bromobenzoate (**104**, 4.32 mL, 6.06 g, 26.4 mmol)¹²⁶ was added followed by PEPPSI-IPr (207 mg, 0.30 mmol, 1 mol%)² and the red solution was stirred for 2 h at room temperature (25 °C) during which time it gradually turns dark grey. Then sat. aq. NH₄Cl (50 mL) was added and the aqueous layer was extracted with EtOAc (3 × 70 mL). The combined organic phases were dried (MgSO₄). Evaporation of the solvents *in vacuo* and purification by column chromatography (*iso*-hexane:EtOAc:NEt₃ = 50:10:1 afforded ethyl 4-(pyridin-3-yl)benzoate (**105**, 5.52 g, 24.3 mmol, 92%) as a yellow solid.¹²⁷

M.p.: 46–48 °C.

¹H NMR (600 MHz, CDCl₃): δ = 8.88 (dd, *J* = 2.3, 1.0 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.21–8.08 (m, 2H), 7.95–7.88 (m, 1H), 7.69–7.59 (m, 2H), 7.40 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 2H).

¹²⁴ A 1 M solution of iodine in THF was prepared in a dry and argon flushed 20 mL Schlenk flask by solving 2.538 g I₂ in 9.30 mL dry THF.

¹²⁵ For the titration accurately weighted aliquots (e.g., 913 mg) of the powder were placed in a dry and argon flushed 20 mL Schlenk flask with a septum and dissolved in ca. 3 mL dry THF. To the solution thus formed, was added the 1 M I₂ solution using a 1 mL NORM-JECT syringe from Henke Sass Wolf until the complete appearance of the dark brown color of iodine (e.g., 1.19 mL equals a concentration of 1.30 mmol/g).

¹²⁶ The following reagents in this section were purchased from commercial sources and used without further purification: Ethyl 4-bromobenzoate (99+%, Apollo Scientific), PEPPSI-IPr (98%, Sigma-Aldrich).

¹²⁷ ISOLUTE® HM-N adsorbed with the crude product is dry-loaded onto a column (diameter: 6.0 cm, height: 25.0 cm) packed with silica gel (250 g) slurry in 50:10:1 *iso*-hexane:EtOAc:NEt₃ (*R_f*(product): 0.12; visualized with UV light) and 100 mL fractions are collected. The desired product is obtained in fractions 21-60, which are concentrated by rotary evaporation (40 °C, 250 mmHg). The purified product is stored under an inert atmosphere in the dark for long-term storage.

^{13}C NMR (150 MHz, CDCl_3): δ = 166.3, 149.1, 148.3, 142.1, 135.8, 134.8, 130.5, 130.3, 127.2, 123.8, 61.3, 14.5.

HRMS (EI): m/z calc. for $[\text{C}_{14}\text{H}_{13}\text{NO}_2]$: 227.0946; found: 227.0934 (M^+).

4.4 Titration of Organozinc Reagents Using Iodine

Accurately weighted aliquots (150–250 mg) of the crude organozinc material were dissolved in dry THF (ca. 1 mL/100 mg). To the resulting solution was added a standard solution of iodine (0.50 M in dry THF), until the color of the iodine remained. Thus, the concentration of the active species (in mmol/g) was determined and thereof the yield of the zinc reagent. In cases where the reaction with iodine was not instantaneous, catalytic amounts of $\text{CuCN} \cdot 2\text{LiCl}$ were added prior to the titration.¹⁰⁶

In some cases the end point of the titration could not be accurately determined due to the orange or brownish color of the zinc reagent. In these cases 2 mL of the 0.25 M (e.g., 0.5 mmol) iodine stock solution were added and the mixture was then stirred 5 min at room temperature. The excess of iodine was then titrated with a stock solution of $\text{Na}_2\text{S}_2\text{O}_3$ in water (0.1 M), therefore the mixture must be vigorously stirred. The amount of active zinc species can then be determined by calculating the difference between the amount of iodine used and the amount of iodine determined by the reverse titration with $\text{Na}_2\text{S}_2\text{O}_3$ (this procedure is referred to as reverse titration).

4.5 Preparation of $\text{Zn}(\text{OPiv})_2$ ¹²⁸

Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL three-necked round-bottom flask, equipped with a magnetic stirring bar, a septum and a pressure equalizer, and was dissolved in dry THF (120 mL). The mixture was cooled to 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol) in dry THF (120 mL) was cannulated to it over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring continued at 25 °C for one additional hour at which point bubbling ceased (a thick slurry was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least 4 h longer. $\text{Zn}(\text{OPiv})_2$ was obtained in quantitative yield, as a puffy amorphous white solid.

4.6 Preparation of $\text{TMPMgCl} \cdot \text{LiCl}$ ¹²⁹

In a dry and argon-flushed Schlenk-flask TMPH (23.6 g, 28.4 mL, 150 mmol) was added to $i\text{PrMgCl} \cdot \text{LiCl}$ (113 mL, 1.26 M in THF, 143 mmol) at 25 °C and the mixture was stirred for 2 days at this temperature. The freshly prepared $\text{TMPMgCl} \cdot \text{LiCl}$ was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator (1.21 M).

¹²⁸ S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, 50, 9205.

¹²⁹ A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, 45, 2958.

4.7 Preparation of $\text{TMPZnOPiv}\cdot\text{Mg}(\text{OPiv})\text{Cl}\cdot\text{LiCl}$ ¹³⁰

A dry and argon flushed 250-mL Schlenk-flask, equipped with a magnetic stirring bar, was charged with a solution of $\text{TMPMgCl}\cdot\text{LiCl}$ (123 mL, 150 mmol) and cooled to 0 °C. Then, solid $\text{Zn}(\text{OPiv})_2$ (42.2 g, 158 mmol, dried *in vacuo* at 300 °C prior to use) was added in one portion and the mixture was allowed to slowly warm up to 25 °C over ca. 1.5 h. Then THF (ca. 10-20 mL) was added to give the base as a bright yellow solution. The freshly prepared $\text{TMPZnOPiv}\cdot\text{Mg}(\text{OPiv})\text{Cl}\cdot\text{LiCl}$ was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator (0.77 M).

4.8 Typical Procedures

Typical procedure for the preparation of the solid organozinc pivalates by magnesium insertion and subsequent transmetalation with $\text{Zn}(\text{OPiv})_2$ (TP1)^{128,131}

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (4.25 g, 175 mmol), LiCl (3.71 g, 87.5 mmol) and THF (140 mL). The aromatic halide (70.0 mmol) was added. If necessary the Schlenk-flask was placed in a water bath for cooling during the initial heat evolution due to the Mg-insertion reaction. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with aq. sat. aq. NH_4Cl solution and/or I_2 . Upon completion of the insertion, solid $\text{Zn}(\text{OPiv})_2$ (23.4 g, 87.5 mmol) was added in one portion. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine in order to determine its actual content in zinc species and the yield of the reaction.

Typical procedure for the preparation of the solid organozinc pivalates by halogen-magnesium exchange and subsequent transmetalation with solid $\text{Zn}(\text{OPiv})_2$ (TP2)^{128,131}

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (70.0 mmol) and dry THF (100 mL). The reaction mixture was cooled to the appropriate temperature, before $i\text{PrMgCl}\cdot\text{LiCl}$ (62.8 mL, 1.17 M, 73.5 mmol) was added dropwise. The progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. aq. NH_4Cl solution and/or I_2 . Upon completion of the exchange, solid $\text{Zn}(\text{OPiv})_2$ (22.5 g, 84.0 mmol) was added in one portion and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine in order to determine its actual content in organozinc species as well as the reaction yield.

¹³⁰ C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302.

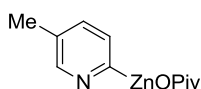
¹³¹ S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289.

Typical procedure for the preparation of the organozinc pivalates by metalation with TMPMgCl·LiCl (2) and subsequent transmetalation with Zn(OPiv)₂ (TP3)^{131,132}

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (70.0 mmol) and dry THF (20 mL). The reaction mixture was cooled to the appropriate temperature, before TMPMgCl·LiCl (63.6 mL, 1.21 M, 77.0 mmol) was added dropwise. The progress of the deprotonation was monitored by GC-analysis of reaction aliquots quenched with I₂. Upon completion of the metalation, solid Zn(OPiv)₂ (22.5 g, 84.0 mmol) was added in one portion and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine in order to determine its actual content in organozinc species as well as the metalation yield.

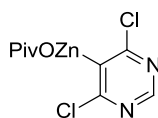
Typical procedure for the preparation of the organozinc pivalates by metalation with TMPZnOPiv·Mg(OPiv)Cl·LiCl (TP4)^{130,131}

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (70.0 mmol) and dry THF (20 mL). The solution was cooled to the given temperature followed by dropwise addition of TMPZnOPiv·Mg(OPiv)Cl·LiCl (130 mL, 0.77 M, 100 mmol) and stirred at the indicated temperature for the given time. Complete metalation was monitored by GC analysis of reaction aliquots, quenched with iodine in dry THF. The solvent was carefully removed *in vacuo* and the dried material was titrated using iodine in order to determine its actual content in organozinc species as well as the metalation yield.

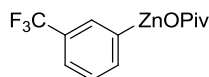
4.9 Preparation of a Set of 17 Polyfunctional Aryl, Benzyl and Heteroarylzinc Pivalates**(5-Methylpyridin-2-yl)zinc Pivalate (106)**

According to **TP2** 2-bromo-5-methylpyridine (1.20 g, 7 mmol) was dissolved in THF (7 mL) and treated with *i*PrMgCl·LiCl (6.27 mL, 1.23 M in THF, 7.7 mmol) at 25 °C for 6 h. Then Zn(OPiv)₂ (2.25 g, 8.4 mmol) was added in one portion and the mixture was stirred until all the salts went in solution (ca. 15 min). After solvent removal *in vacuo* zinc reagent **106** (5.56 g) was obtained as a light yellow solid. The content of active zinc species was determined by titration of 281 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.87 mmol/g was determined which corresponds to a yield of 71%.

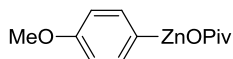
¹³² C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428.

(4,6-Dichloropyrimidin-5-yl)zinc Pivalate (107)

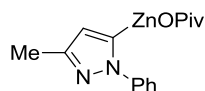
According to **TP4** 4,6-dichloropyrimidine (1.04 g, 7 mmol) was treated with $\text{TMPZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{Cl} \cdot \text{LiCl}$ (7.78 mL, 0.99 M in THF, 7.7 mmol) at 25 °C for 30 min. After solvent removal *in vacuo* zinc reagent **107** (6.06 g) was obtained as a light orange solid. The content of active zinc species was determined by titration of 140 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.96 mmol/g was determined which corresponds to a yield of 86%.

(3-(Trifluoromethyl)phenyl)zinc Pivalate (108)

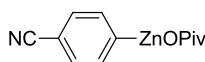
According to **TP2** 1-bromo-3-(trifluoromethyl)benzene (1.58 g, 7.00 mmol) was dissolved in dry THF (10 mL) and treated with $i\text{PrMgCl} \cdot \text{LiCl}$ (6.27 mL, 1.23 M in THF, 7.70 mmol) at 0 °C for 8 h. Then $\text{Zn}(\text{OPiv})_2$ (2.25 g, 8.40 mmol) was added in one portion and the mixture was slowly warmed to room temperature and was stirred until all the salts went in solution (ca. 15 min). After solvent removal *in vacuo* zinc reagent **108** (4.79 g) was obtained as a white solid. The content of active zinc species was determined by titration of 270 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 1.35 mmol/g was determined which corresponds to a yield of 92%.

(4-Methoxyphenyl)zinc Pivalate (109)

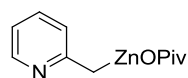
According to **TP1** LiCl (371 mg, 8.75 mmol) and $\text{Zn}(\text{OPiv})_2$ (2.34 g, 8.75 mmol) were dissolved in dry THF (14 mL). After addition of Mg turnings (425 mg, 17.5 mmol), 1-bromo-4-methoxybenzene (1.31 g, 7 mmol) was added at 25 °C and the reaction mixture was stirred at 50 °C for 15 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **109** was obtained as a white solid (4.76 g). The content of active zinc species was determined by titration of 282 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 1.22 mmol/g was determined which corresponds to a yield of 83%.

(3-Methyl-1-phenyl-1H-pyrazol-5-yl)zinc Pivalate (110)

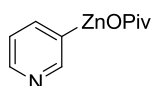
According to **TP1** Mg turnings (425 mg, 17.5 mmol) and Zn(OPiv)_2 (2.34 g, 8.75 mmol) were suspended in dry THF (14 mL). After addition of 5-chloro-3-methyl-1-phenyl-1H-pyrazole (1.35 g, 7 mmol) the reaction mixture was stirred at 25 °C for 15 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **110** was obtained as a white solid (6.41 g). The content of active zinc species was determined by titration of 222 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.75 mmol/g was determined which corresponds to a yield of 69%.

(4-Cyanophenyl)zinc Pivalate (111)

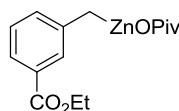
According to **TP2** 4-bromobenzonitrile (1.27 g, 7.00 mmol) was dissolved in THF (10 mL) and treated with *i*PrMgCl·LiCl (6.00 mL, 1.23 M in THF, 7.35 mmol) at 0 °C for 15 h. Then Zn(OPiv)_2 (2.25 g, 8.40 mmol) was added in one portion and the mixture was slowly warmed to room temperature and was stirred until all the salts went in solution (ca. 15 min). After solvent removal *in vacuo* zinc reagent **111** (5.40 g) was obtained as a white solid. The content of active zinc species was determined by titration of 241 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 1.09 mmol/g was determined which corresponds to a yield of 84%.

(Pyridin-2-ylmethyl)zinc Pivalate (112)

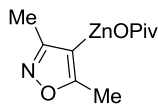
According to **TP4** 2-picoline (559 mg, 6.00 mmol) was treated with $\text{TMPZnOPiv} \cdot \text{Mg(OPiv)Cl} \cdot \text{LiCl}$ (6.67 mL, 0.99 M in THF, 6.60 mmol) at 25 °C for 1 h. After solvent removal *in vacuo* zinc reagent **112** (5.63 g) was obtained as a light orange solid. The content of active zinc species was determined by titration of 155 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.76 mmol/g was determined which corresponds to a yield of 71%.

(Pyridin-3-yl)zinc Pivalate (113)

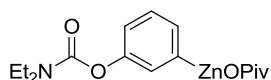
According to **TP2** 3-bromopyridine (1.11 g, 7.00 mmol) was dissolved in THF (14 mL) and treated with *i*PrMgCl·LiCl (6.27 mL, 1.23 M in THF, 7.70 mmol) at 0 °C for 1 h. Then Zn(OPiv)₂ (2.25 g, 8.40 mmol) was added in one portion and the mixture was slowly warmed to room temperature and was stirred until all the salts went in solution (ca. 15 min). After solvent removal *in vacuo* zinc reagent **113** (4.50 g) was obtained as a light brown solid. The content of active zinc species was determined by titration of 134 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 1.40 mmol/g was determined which corresponds to a yield of 90%.

(3-(Ethoxycarbonyl)benzyl)zinc Pivalate (114)

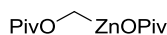
According to **TP1** Mg turnings (425 mg, 17.5 mmol) and Zn(OPiv)₂ (2.34 g, 8.75 mmol) were suspended in dry THF (14 mL). After addition of ethyl 3-(chloromethyl)benzoate (1.39 g, 7.00 mmol) the reaction mixture was stirred at 25 °C for 15 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **114** was obtained as an orange solid (6.01 g). To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 120 mg of zinc reagent **114** in dry THF (1.2 mL). After stirring this mixture for 5 min at 25 °C the excess of iodine was determined by titration with a 0.1 M stock solution of Na₂S₂O₃ (see above). A concentration of 0.71 mmol/g was determined which corresponds to a yield of 61%.

(3,5-Dimethylisoxazol-4-yl)zinc Pivalate (115)

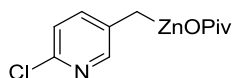
According to **TP1** LiCl (371 mg, 8.75 mmol) and Zn(OPiv)₂ (2.34 g, 8.75 mmol) were dissolved in dry THF (14 mL). After addition of Mg turnings (425 mg, 17.5 mmol), 4-bromo-3,5-dimethylisoxazole (1.23 g, 7.00 mmol) was added at 25 °C and the reaction mixture was stirred at the same temperature for 2 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **115** was obtained as a grey solid (5.47 g). The content of active zinc species was determined by titration of 197 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.99 mmol/g was determined which corresponds to a yield of 77%.

(3-((Diethylcarbamoyl)oxy)phenyl)zinc Pivalate (116)

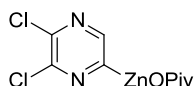
According to **TP1** LiCl (371 mg, 8.75 mmol) and Zn(OPiv)₂ (2.34 g, 8.75 mmol) were dissolved in dry THF (14 mL). After addition of Mg turnings (425 mg, 17.5 mmol), 4-bromo-3,5-dimethylisoxazole (1.23 g, 7.00 mmol) was added at 25 °C and the reaction mixture was stirred at the same temperature for 4 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **116** was obtained as a yellow solid (6.17 g). The content of active zinc species was determined by titration of 298 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 0.79 mmol/g was determined which corresponds to a yield of 70%.

(Pivaloyloxy)methylzinc Pivalate (117)

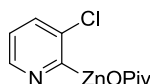
According to **TP2** iodomethyl pivalate (1.69 g, 7.00 mmol) was dissolved in THF (14 mL) and treated with *i*PrMgCl·LiCl (6.27 mL, 1.23 M in THF, 7.70 mmol) at -78 °C for 15 min. Then Zn(OPiv)₂ (2.25 g, 8.40 mmol) was added in one portion and the mixture was stirred at the same temperature for 30 min, slowly warmed to room temperature and stirred until all the salts went in solution. After solvent removal *in vacuo* zinc reagent **117** (5.33 g) was obtained as a white solid. The content of active zinc species was determined by titration of 161 mg of the reagent with a stock solution of iodine (0.25 M in THF). A concentration of 1.14 mmol/g was determined which corresponds to a yield of 87%.

((6-Chloropyridin-3-yl)methylzinc Pivalate (118)

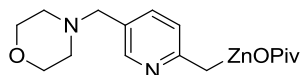
According to **TP1** LiCl (371 mg, 8.75 mmol) and Zn(OPiv)₂ (2.34 g, 8.75 mmol) were dissolved in dry THF (14 mL). After addition of Mg turnings (425 mg, 17.5 mmol), 2-chloro-5-(chloromethyl)pyridine (1.13 g, 7.00 mmol) was added at 25 °C and the reaction mixture was stirred at the same temperature for 6 h. After subsequent cannulation to another argon-flushed *Schlenk*-tube the solvent was removed *in vacuo*. Zinc reagent **118** was obtained as a brown solid (5.40 g). To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 198 mg of the reagent in dry THF (2.0 mL). After stirring this mixture for 5 min at 25 °C the excess of iodine was determined by titration with a 0.1 M stock solution of Na₂S₂O₃ (see above). A concentration of 0.98 mmol/g was determined which corresponds to a yield of 76%.

(5,6-Dichloropyrazin-2-yl)zinc Pivalate (119)

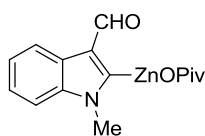
According to **TP3** 2-picoline (559 mg, 6.00 mmol) was treated with $\text{TMPMgCl} \cdot \text{LiCl}$ (6.94 mL, 1.11 M in THF, 7.70 mmol) at $-45\text{ }^{\circ}\text{C}$ for 2 h. Then $\text{Zn}(\text{OPiv})_2$ (2.25 g, 8.40 mmol) was added in one portion and the mixture was slowly warmed to room temperature and was stirred until all the salts went in solution. After solvent removal *in vacuo* zinc reagent **119** (5.90 g) was obtained as a brown solid. To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 255 mg of zinc reagent **119** in dry THF (2.5 mL). After stirring this mixture for 5 min at $25\text{ }^{\circ}\text{C}$ the excess of iodine was determined by titration with a 0.1 M stock solution of $\text{Na}_2\text{S}_2\text{O}_3$ (see above). A concentration of 1.12 mmol/g was determined which corresponds to a yield of 94%.

(3-Chloropyridin-2-yl)zinc Pivalate (120)

According to **TP4** 3-chloropyridine (795 mg, 7.00 mmol) was treated with $\text{TMPZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{Cl} \cdot \text{LiCl}$ (11.4 mL, 0.92 M in THF, 10.5 mmol) at $50\text{ }^{\circ}\text{C}$ for 1.5 h. After solvent removal *in vacuo* zinc reagent **120** (6.33 g) was obtained as a light brown solid. To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 254 mg of zinc reagent **120** in dry THF (2.5 mL). After stirring this mixture for 5 min at $25\text{ }^{\circ}\text{C}$ the excess of iodine was determined by titration with a 0.1 M stock solution of $\text{Na}_2\text{S}_2\text{O}_3$ (see above). A concentration of 1.04 mmol/g was determined which corresponds to a yield of 94%.

((5-(Morpholinomethyl)pyridin-2-yl)methyl)zinc Pivalate (121)

According to **TP4** 4-((6-methylpyridin-3-yl)methyl)morpholine (1.20 g, 7.00 mmol) was treated with $\text{TMPZnOPiv} \cdot \text{Mg}(\text{OPiv})\text{Cl} \cdot \text{LiCl}$ (8.06 mL, 0.93 M in THF, 7.5 mmol) at $50\text{ }^{\circ}\text{C}$ for 2 h. After solvent removal *in vacuo* zinc reagent **121** (6.30 g) was obtained as a light brown solid. To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 163 mg of **121** in dry THF (1.6 mL). After stirring this mixture for 5 min at $25\text{ }^{\circ}\text{C}$ the excess of iodine was determined by titration with a 0.1 M stock solution of $\text{Na}_2\text{S}_2\text{O}_3$ (see above). A concentration of 0.74 mmol/g was determined which corresponds to a yield of 75%.

(3-Formyl-1-methyl-1H-indol-2-yl)zinc Pivalate (122)

According to **TP4** 1-methyl-1*H*-indole-3-carbaldehyde (1.11 g, 7.00 mmol) in THF (7 mL) was treated with $\text{TMPZnOPiv} \cdot \text{Mg(OPiv)Cl} \cdot \text{LiCl}$ (9.10 mL, 0.85 M, 7.70 mmol) at 25 °C and stirred at this temperature for 0.5 h. After solvent removal *in vacuo* zinc reagent **122** (6.97 g) was obtained as a yellow solid. To determine the content of active zinc species 2.00 mL of an iodine stock solution (0.25 M) were added to a solution of 295 mg of **122** in dry THF (3.0 mL). After stirring this mixture for 5 min at 25 °C the excess of iodine was determined by titration with a 0.1 M stock solution of $\text{Na}_2\text{S}_2\text{O}_3$ (see above). A concentration of 0.89 mmol/g was determined which corresponds to a yield of 88%.

5 Regioselective Transition-Metal-Free Allyl–Allyl Cross-Couplings

Zinc dust (> 98%) was obtained from Sigma Aldrich. Following compounds were prepared according to literature procedures: ethyl 5-chlorocyclopent-1-enecarboxylate,¹³³ (*E*)-1-bromonon-2-ene (**124a**),¹³⁴ *tert*-butyl 2-(bromomethyl)acrylate (**124c**),¹³⁵ 5-bromocyclopent-1-enecarbonitrile (**124d**),¹³⁶ ethyl 2-(bromomethyl)acrylate (**124e**),¹³⁷ ethyl 6-bromocyclohex-1-enecarboxylate (**124f**),¹³⁸ (*E*)-(3-bromoprop-1-en-1-yl)trimethylsilane (**124g**),¹³⁹ (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (**124i**),¹⁴⁰ (*E*)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene (**124j**),¹⁴¹ (*Z*)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene (**124k**),¹⁴¹ (3-chloroprop-1-yn-1-yl)trimethylsilane (**126a**),¹⁴² ethyl 7-bromohept-5-ynoate (**126b**),¹⁴³ 1,4-dibromobut-2-yne (**126c**).¹⁴⁴

5.1 Titration of Organozinc Reagents Using Iodine

A dry flask was charged with accurately weighed I₂ (63.5 mg, 0.25 mmol), fitted with a rubber septum, and flushed with argon. THF (3–5 mL) was added and stirring was started. After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C in an ice bath and the organozinc reagent was added dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared.¹⁰⁶

¹³³ Z. Peng, T. D. Blümke, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 8516.

¹³⁴ J. Tan, C.-H. Cheon, H. Yamamoto, *Angew. Chem. Int. Ed.* **2012**, *51*, 8264.

¹³⁵ A. Bergmann, O. Reiser, *Chem. Eur. J.* **2014**, *20*, 7613.

¹³⁶ J.-B. Langlois, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 447.

¹³⁷ J. Villieras, M. Rambaud, *Synthesis* **1982**, 924.

¹³⁸ C. Sämann, P. Knochel, *Synthesis* **2013**, 1870.

¹³⁹ D. J. Vyas, M. Oestreich, *Chem. Commun.* **2010**, *46*, 568.

¹⁴⁰ A. F. Barrero, M. M. Herrador, J. F. Q. del Moral, P. Arteaga, J. F. Arteaga, M. Piedra, E. M. Sánchez, *Org. Lett.* **2005**, *7*, 2301.

¹⁴¹ J. M. Takacs, Y. Myoung, L. G. Anderson, *J. Org. Chem.* **1994**, *59*, 6928.

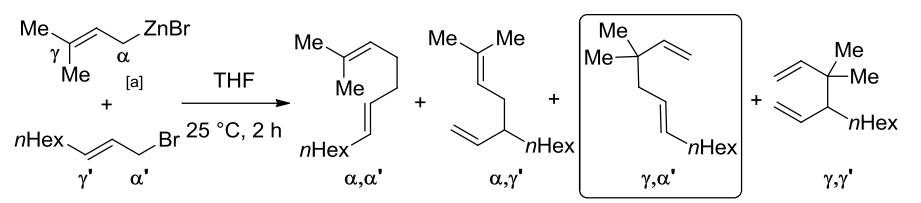
¹⁴² T. Baker, C. Britton, *Org. Lett.* **2007**, *9*, 45.

¹⁴³ K. Belyk, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1992**, *57*, 4070.

¹⁴⁴ A. Geny, N. Ageton, L. Iannazzo, M. Malacria, C. Aubert, V. Gandon, *Angew. Chem. Int. Ed.* **2009**, *48*, 1810.

5.2 Cosolvent Evaluation for the Allyl-Allyl Cross-Coupling

Table 13: Optimization of the conditions for the allyl-allyl cross-coupling



Entry	Temp. [°C]	Cosolvent ^[b]	α, α'	α, γ	γ, α'	γ, γ'	Yield ^[c] [%]
1	25	none	33	25	35	7	75
2	-10	none	57	27	10	6	65
3	-40	none	88	8	4	0	61
4	25	toluene	4	5	89	2	94
5	25	<i>n</i> -hexane	16	2	82	0	82
6	25	1,4-dioxane	5	10	81	4	92
7	25	DMSO	0	5	91	4	100
8	25	NMP	0	5	95	0	100
9	25	DMPU	0	0	100	0	100
10	25	DMPU ^[d]	10	15	71	4	100

[a] LiCl is omitted for clarity. [b] A 1:1 mixture with THF was used. [c] Determined by GC-analysis using undecane as an internal standard. [d] DMPU was just used as an additive (3.0 equiv. in respect to the organozinc).

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, (*E*)-1-bromonon-2-ene (**124a**, 51.3 mg, 0.25 mmol) was dissolved in the corresponding cosolvent (0.79 mL). Prenylzinc bromide (**123a**) in dry THF (0.38 M in THF, 0.79 mL, 0.30 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature. The resulting $\alpha, \alpha' / \alpha, \gamma' / \gamma, \alpha' / \gamma, \gamma'$ ratio and the yield were determined by GC-analysis using undecane as an internal standard (retention time of isolated compounds as reference).

5.3 Typical Procedures

Typical Procedure for the Preparation of the Allylzinc Halides of Type 123 (TP1):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (466 mg, 11.0 mmol). The flask was heated to 450 °C for 10 min (heat gun) under high vacuum followed by the addition of zinc dust (1.31 g, 20.0 mmol). The vessel was evacuated and refilled with argon. THF (10 mL) and 1,2-dibromoethane (215 μ L, 2.50 mmol) were added via syringe and the reaction mixture was heated to 50 °C until bubbling occurred. The allylic halide (10.0 mmol) was added dropwise as a solution in THF (10 mL) over a period of 15 min. The mixture was stirred for the given

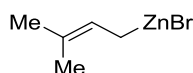
time at room temperature before the zinc powder was allowed to settle down. The supernatant solution was carefully filtrated using a syringe filter and the yield of the resulting solution of the allylzinc halide was determined by iodometric titration.

Typical Procedure for the Allyl-Allyl-Coupling of the Allylzinc Halides of Type 123 with Allylic Halides of Type 124 (TP2):

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, the allylic halide (1.0 equiv) was dissolved in dry DMPU (1 M). The allylic zinc halide (1.20 equiv) was added dropwise and the mixture was stirred for 1 h at room temperature. Then a sat. aq. NH_4Cl solution (5 mL) was added, the aqueous layer was extracted with EtOAc (3×10 mL), washed with solutions of NaHCO_3 (5 mL, sat. aq.) and NaCl (5 mL, sat. aq.) and the combined organic phases were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected products of type 125.

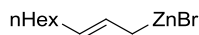
5.4 Preparation of the Allylzinc Halides

Prenylzinc Bromide (123a)

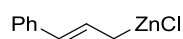


According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added prenyl bromide (1.49 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration prenylzinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.36 mmol/mL, which corresponds to a yield of 72% was determined.

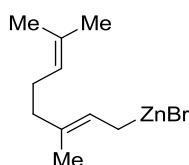
(*E*)-Non-2-en-1-ylzinc Bromide (123b)



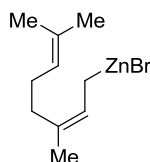
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added (*E*)-non-2-en-1-yl bromide (2.05 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration (*E*)-non-2-en-1-ylzinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.35 mmol/mL, which corresponds to a yield of 77% was determined.

Cinnamylzinc Chloride (123c)

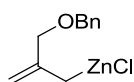
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added cinnamylchloride (1.52 g, 10.0 mmol) in THF (10 mL). After 2 h at 25 °C and subsequent filtration cinnamyl zinc chloride was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.43 mmol/mL, which corresponds to a yield of 86% was determined.

Geranylzinc Bromide (123d)

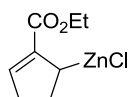
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added geranyl bromide (2.17 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration geranylzinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.42 mmol/mL, which corresponds to a yield of 83% was determined.

Nerylzinc Bromide (123e)

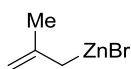
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added neryl bromide (2.17 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration nerylzinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.24 mmol/mL, which corresponds to a yield of 58% was determined.

(2-((Benzyloxy)methyl)allyl)zinc Chloride (123f)

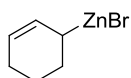
According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added (((2-(chloromethyl)allyl)oxy)methyl)benzene (1.97 g, 10.0 mmol) in THF (10 mL). After 8 h at 50 °C and subsequent filtration (2-((benzyloxy)methyl)allyl)zinc chloride was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.19 mmol/mL, which corresponds to a yield of 41% was determined.

(2-(Ethoxycarbonyl)cyclopent-2-en-1-yl)zinc Chloride (123g)

According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added 5-chlorocyclopent-1-enecarboxylate (1.75 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C and subsequent filtration (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc chloride was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.29 mmol/mL, which corresponds to a yield of 60% was determined.

(2-Methylallyl)zinc Bromide (123h)

According to **TP1** to a mixture of zinc dust (655 mg, 10.0 mmol), LiCl (233 mg, 5.5 mmol) and THF (5 mL) was added 3-bromo-2-methylprop-1-ene (675 mg, 5.00 mmol) in THF (5 mL). After 1 h at 25 °C and subsequent filtration (2-methylallyl)zinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.30 mmol/mL, which corresponds to a yield of 66% was determined.

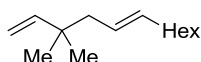
Cyclohex-2-en-1-ylzinc Bromide (123i)

According to **TP1** to a mixture of zinc dust (1.31 g, 20.0 mmol), LiCl (466 mg, 11.0 mmol) and THF (10 mL) was added 3-bromocyclohex-1-ene (1.61 g, 10.0 mmol) in THF (10 mL). After 1 h at 25 °C

and subsequent filtration cyclohex-2-en-1-ylzinc bromide was obtained as a solution in THF. The content of active zinc species was determined by titration with a stock solution of iodine (1.00 M in THF). A concentration of 0.45 mmol/mL, which corresponds to a yield of 89% was determined.

5.5 Preparation of the Allyl-Allyl-Coupling Products

(*E*)-3,3-Dimethyldodeca-1,5-diene (γ,α' -125a)



According to **TP2** prenylzinc bromide in dry THF (0.35 M in THF, 1.70 mL, 0.60 mmol) was added to (*E*)-1-bromonon-2-ene (103 mg, 0.50 mmol) in DMPU (1.70 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (90 mg, 0.46 mmol, 93%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.80 (dd, J = 17.8, 10.4 Hz, 1H), 5.43–5.30 (m, 2H), 4.91 (m, 1H), 4.87 (m, 1H), 2.06–1.93 (m, 4H), 1.22–1.17 (m, 8H), 0.96 (s, 6H), 0.88 (t, J = 6.6 Hz, 3H).

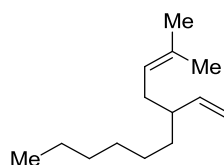
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 148.5, 133.1, 126.5, 110.0, 45.7, 32.6, 31.7, 29.7, 29.6, 28.8, 26.5, 22.7, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2957 (s), 2907 (vs), 2853 (s), 1746 (w), 1639 (m), 1462 (m), 1413 (w), 1378 (m), 1362 (w), 1237 (w), 1047 (w), 998 (m), 968 (vs), 909 (vs), 723 (m), 684 (m).

MS (EI, 70 eV): m/z (%) = 179.3 (1), 151.2 (8), 124.2 (2), 69.1 (100), 55.1 (11), 41.0 (30).

HRMS (EI): m/z calc. for [C₁₄H₂₆]⁺: 194.2040; found 194.2026.

2-Methyl-5-vinylundec-2-ene (α,γ' -125a)



According to **TP2** (*E*)-non-2-en-1-ylzinc bromide in dry THF (0.36 M, 1.70 mL, 0.60 mmol) was added to prenyl bromide (74 mg, 0.50 mmol) in DMPU (1.70 mL) and the mixture was stirred for 24 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (76 mg, 0.39 mmol, 78% (97:3:0:0)).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.68–5.51 (m, 1H), 5.16–5.05 (m, 1H), 5.01–4.86 (m, 2H), 2.14–1.86 (m, 3H), 1.70 (d, J = 1.4 Hz, 2H), 1.60 (d, J = 1.4 Hz, 3H), 1.49–1.11 (m, 10H), 0.96–0.80 (m, 3H).

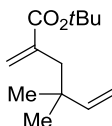
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 143.5, 132.1, 122.9, 113.8, 44.5, 34.4, 33.7, 32.0, 29.6, 27.3, 25.9, 22.8, 18.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2956, 2908, 2854, 1641, 1461, 1378, 1069, 965, 910.

MS (EI, 70 eV): m/z (%) = 194.2 (M^+ , 2), 151.2 (18), 109.2 (10), 69.2 (100).

HRMS (EI): m/z calc. for $[C_{14}H_{26}]$: 194.2035; found: 194.2034 (M^+).

***tert*-butyl 4,4-dimethyl-2-methylenhex-5-enoate (125b)**



According to **TP2** prenylzinc bromide in dry THF (0.39 M, 1.9 mL, 0.75 mmol) was added to *tert*-butyl 2-(bromomethyl)acrylate (133 mg, 0.6 mmol) in DMPU (1.9 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane:Et₂O 20:1) afforded the title compound as a colorless oil (104 mg, 0.49 mmol, 82%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 6.07 (s, 1H), 5.79 (m, 1H), 5.35 (s, 1H), 4.88 (s, 1H), 4.85 (d, J = 4.2, 1H), 2.32 (s, 2H), 1.47 (s, 9H), 0.98 (s, 6H).

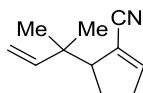
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 167.4, 147.7, 139.7, 126.4, 110.7, 80.5, 43.5, 37.5, 28.1, 26.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 668 (vw), 687 (w), 751 (w), 761 (w), 816 (m), 851 (m), 870 (w), 886 (w), 909 (m), 942 (w), 1000 (w), 1007 (w), 1047 (vw), 1127 (s), 1151 (vs), 1210 (w), 1255 (w), 1288 (w), 1311 (w), 1343 (w), 1367 (m), 1380 (w), 1392 (w), 1415 (w), 1458 (w), 1474 (w), 1628 (w), 1640 (w), 1712 (s), 2871 (vw), 2931 (w), 2966 (w).

MS (EI, 70 eV): m/z (%) = 154.1 (8), 137.1 (12), 112.1 (15), 69.1 (100), 57.1 (63), 41.0 (37).

HRMS (EI): m/z calc. for $[C_9H_{14}O_2]^+$: 154.0994; found: 154.0998 ($M - tBu + H^+$).

5-(2-Methylbut-3-en-2-yl)cyclopent-1-ene-1-carbonitrile (125c)



According to **TP2** prenylzinc bromide in dry THF (0.35 M in THF, 1.70 mL, 0.60 mmol) was added to 5-bromocyclopent-1-ene-1-carbonitrile (86 mg, 0.50 mmol) in DMPU (1.70 mL) and the mixture was stirred for 24 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (73 mg, 0.45 mmol, 91%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 6.70 (td, J = 2.7, 1.8 Hz, 1H), 5.77 (dd, J = 17.7, 10.5 Hz, 1H), 5.02–4.90 (m, 2H), 2.82–2.71 (m, 1H), 2.43–2.25 (m, 2H), 2.00–1.84 (m, 1H), 1.80–1.64 (m, 1H), 1.04 (s, 6H).

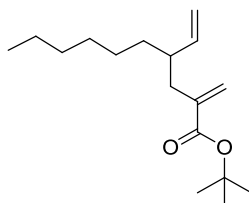
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 152.5, 145.4, 118.2, 116.7, 112.7, 56.6, 40.4, 33.0, 26.3, 25.0, 24.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2966 (s), 2917 (s), 2217 (m), 1726 (vs), 1657 (m), 1474 (s), 1410 (s), 1367 (s), 1266 (s), 1170 (vs), 1045 (vs), 917 (vs), 801 (s).

MS (EI, 70 eV): m/z (%) = 161.3 (4), 104.2 (2), 93.2 (7), 69.1 (100).

HRMS (EI): m/z calc. for $[C_7H_6N]^+$: 161.1199; found 161.1204.

***tert*-Butyl 2-methylene-4-vinyldecanoate (125d)**



According to **TP2** (*E*)-oct-2-en-1-ylzinc bromide in dry THF (0.30 M, 2.00 mL, 0.60 mmol) was added to *tert*-butyl 2-(bromomethyl)acrylate (96.5 mg, 0.50 mmol) in DMPU (0.5 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (122 mg, 0.46 mmol, 92%).

^1H -NMR (400 MHz, CDCl_3): δ / ppm = 6.05 (d, J = 1.8 Hz, 1H), 5.50 (ddd, J = 17.1, 10.3, 8.4 Hz, 1H), 5.42–5.33 (m, 1H), 4.99–4.81 (m, 2H), 2.43–2.27 (m, 1H), 2.26–2.11 (m, 2H), 1.48 (s, 9H), 1.43–1.14 (m, 10H), 0.94–0.80 (m, 3H).

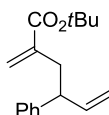
^{13}C -NMR (101 MHz, CDCl_3): δ / ppm = 166.8, 142.5, 140.9, 125.1, 114.7, 80.5, 43.5, 38.1, 34.8, 32.0, 29.5, 28.2, 27.2, 22.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2926, 2856, 1712, 1632, 1457, 1419, 1392, 1367, 1340, 1309, 1253, 1212, 1150, 1112, 1037, 994, 939, 910, 877, 852, 816, 760, 724, 698.

MS (EI, 70 eV): m/z (%) = 210 (M-*t*Bu, 62), 193 (15), 165 (M-CO₂*t*Bu, 57), 139 (33), 122 (39), 111 (33), 95 (34), 83 (39), 69 (50), 57 (100).

HRMS (EI): m/z calc. for $[C_{13}H_{22}O_2]$: 210.1620; found: 210.1643 (M-*t*Bu).

***tert*-Butyl 2-methylene-4-phenylhex-5-enoate (125e)**



According to **TP2** (3-Phenylprop-2-enyl)zinc chloride in dry THF (0.31 M in THF, 3.90 mL, 1.20 mmol) was added to *tert*-butyl(2-bromomethyl)acrylate (221 mg, 1.00 mmol) in DMPU (1.00 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 100:1) afforded the title compound as a colorless oil (250 mg, 0.96 mmol, 96%).

^1H -NMR (300 MHz, CDCl_3): δ / ppm = 7.35–7.24 (m, 2H), 7.23–7.09 (m, 3H), 6.03 (d, J = 1.6 Hz, 1H), 6.01–5.90 (m, 1H), 5.31 (dd, J = 2.7, 1.1 Hz, 1H), 5.08–4.95 (m, 2H), 3.56 (q, J = 7.7 Hz, 1H), 2.77–2.59 (m, 2H), 1.49 (s, 9H).

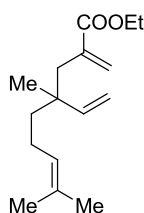
^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 166.5, 143.8, 141.3, 140.1, 128.6, 127.9, 126.4, 126.0, 114.9, 80.6, 49.1, 38.7, 28.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3026, 2976, 2891, 1706, 1631, 1600, 1491, 1477, 1452, 1391, 1366, 1337, 1305, 1250, 1211, 1142, 1075, 1030, 991, 941, 912, 877, 815, 786, 752, 698, 665.

MS (EI, 70 eV): m/z (%) = 258.1 (M, 1), 202.0 (20), 185.0 (M - $t\text{BuO}$, 15), 141.0 (5), 117.0 (100).

HRMS (EI): m/z calc. for $[\text{C}_{13}\text{H}_{13}\text{O}]^+$: 185.0966; found: 185.0960 ($[\text{M}-\text{OtBu}]^+$).

Ethyl 4,8-Dimethyl-2-methylene-4-vinylnon-7-enoate (125f)



According to **TP2** geranylzinc bromide in dry THF (0.37 M, 1.40 mL, 0.45 mmol) was added to ethyl 2-(bromomethyl)acrylate (97 mg, 0.50 mmol) in DMPU (1.35 mL) and the mixture was stirred for 12 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (115 mg, 0.46 mmol, 92%).

^1H -NMR (400 MHz, CDCl_3): δ / ppm = 6.13 (d, J = 1.8 Hz, 1H), 5.69 (dd, J = 17.5, 10.8 Hz, 1H), 5.41 (dt, J = 1.7, 0.9 Hz, 1H), 5.11–5.02 (m, 1H), 4.95 (dd, J = 10.8, 1.4 Hz, 1H), 4.83 (dd, J = 17.5, 1.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.43 (dd, J = 13.2, 0.9 Hz, 1H), 2.32 (dd, J = 13.2, 0.9 Hz, 1H), 1.98–1.81 (m, 2H), 1.72–1.61 (m, 3H), 1.57 (s, 3H), 1.42–1.20 (m, 5H), 0.93 (s, 3H).

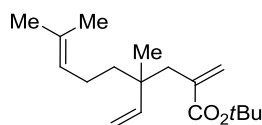
^{13}C -NMR (101 MHz, CDCl_3): δ / ppm = 168.3, 145.9, 138.3, 131.3, 127.1, 124.9, 112.3, 60.7, 42.6, 41.1, 40.6, 25.8, 23.1, 21.2, 17.7, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2969 (m), 2917 (m), 1717 (vs), 1627 (m), 1445 (m), 1413 (m), 1369 (m), 1177 (vs), 1147 (s), 1115 (s), 1028 (m), 1003 (m), 942 (m), 911 (s), 857 (w), 815 (m), 754 (w).

MS (EI, 70 eV): m/z (%) = 250.3 (M^+ , 1), 207.3 (7), 137.2 (22), 69.1 (100).

HRMS (EI): m/z calc. for $[\text{C}_{16}\text{H}_{26}\text{O}_2]^+$: 250.1933; found 250.1933.

tert-butyl 4,8-dimethyl-2-methylene-4-vinylnon-7-enoate (125g)



According to **TP2** geranylzinc bromide in dry THF (0.29 M, 1.7 mL, 0.5 mmol) was added to *tert*-butyl 2-(bromomethyl)acrylate (88 mg, 0.4 mmol) in DMPU (1.7 mL) and the mixture was stirred for 3 h at

room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (100 mg, 0.36 mmol, 90%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 6.06 (d, J =2.0, 1H), 5.70 (dd, J =17.5, 10.8, 1H), 5.34 (dd, J =2.0, 1.0, 1H), 5.10–5.03 (m, 1H), 4.95 (dd, J =10.8, 1.4, 1H), 4.85 (dd, J =17.5, 1.4, 1H), 2.39 (dd, J =13.1, 0.9, 1H), 2.28 (dd, J =13.1, 0.9, 1H), 1.93–1.83 (m, 2H), 1.66 (d, J =1.3, 3H), 1.59–1.54 (m, 4H), 1.47 (s, 9H), 1.35–1.28 (m, 2H), 0.94 (s, 3H).

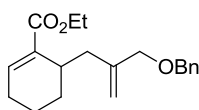
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 167.5, 146.0, 139.6, 131.3, 126.4, 125.0, 112.3, 80.5, 42.6, 41.2, 40.6, 28.1, 25.8, 23.1, 21.2, 17.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 666 (w), 760 (w), 783 (w), 802 (w), 815 (m), 833 (w), 852 (m), 874 (w), 888 (w), 910 (m), 940 (m), 987 (w), 1003 (m), 1118 (m), 1147 (vs), 1208 (w), 1254 (m), 1294 (m), 1306 (w), 1345 (w), 1367 (m), 1392 (m), 1414 (w), 1455 (m), 1478 (w), 1548 (w), 1628 (w), 1662 (w), 1712 (s), 2920 (w), 2971 (w), 3083 (vw).

MS (EI, 70 eV): m/z (%) = 222.2 (11), 179.1 (22), 137.1 (29), 82.1 (26), 81.1 (56), 69.1 (100).

HRMS (EI): m/z calc. for [C₁₄H₂₂O₂]⁺: 222.1630; found: 222.1611 (M-*t*Bu+H⁺).

Ethyl 6-(2-(Benzyloxy)allyl)cyclohex-1-enecarboxylate (125h)



According to **TP2** (2-((benzyloxy)methyl)allyl)zinc chloride in dry THF (0.21 M, 3.33 mL, 0.70 mmol) was added to ethyl 6-bromocyclohex-1-enecarboxylate (135 mg, 0.58 mmol) in DMPU (3.3 mL) and the mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane:Et₂O 20:1) afforded the title compound as a colorless oil (157 mg, 0.523 mmol, 90%).

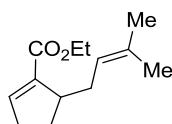
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.33–7.24 (m, 4H), 7.24–7.17 (m, 1H), 6.71 (td, J = 2.6, 1.4 Hz, 1H), 5.09–5.01 (m, 1H), 4.92–4.85 (m, 1H), 4.45 (d, J = 1.3 Hz, 2H), 4.18–4.04 (m, 2H), 3.93 (s, 2H), 3.14–3.02 (m, 1H), 2.59–2.50 (m, 1H), 2.50–2.24 (m, 2H), 2.06–1.93 (m, 1H), 1.92–1.81 (m, 1H), 1.75–1.65 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 165.2, 144.9, 143.9, 140.1, 138.6, 128.4, 127.7, 127.6, 112.8, 73.1, 72.1, 60.1, 42.3, 37.7, 31.5, 29.2, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3422, 3065, 2938, 2361, 1714, 1654, 1603, 1584, 1559, 1540, 1496, 1452, 1371, 1270, 1205, 1176, 1095, 1070, 1025, 914, 860, 828, 749, 714, 698, 668, 648.

MS (EI, 70 eV): m/z (%) = 300 (M⁺, 1), 255 (2), 194 (9), 163 (19), 139 (20), 117 (11), 91 (100), 67 (13).

HRMS (EI): m/z calc. for [C₁₈H₂₁O₃]⁺: 285.1491; found 285.2805 (M-Me).

Ethyl 5-(3-Methylbut-2-en-1-yl)cyclopent-1-enecarboxylate (125i)

According to **TP2** (2-(ethoxycarbonyl)cyclopent-2-en-1-yl)zinc chloride in dry THF (0.23 M, 4.35 mL, 1.00 mmol) was added to prenyl bromide (119 mg, 0.80 mmol) in DMPU (4.35 mL) and the mixture was stirred for 12 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (139 mg, 0.67 mmol, 84%).

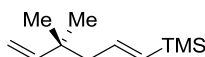
¹H-NMR (800 MHz, CDCl₃): δ / ppm = 6.79 (td, J = 2.6, 1.4 Hz, 1H), 5.19–5.10 (m, 1H), 4.27–4.15 (m, 2H), 3.04–2.95 (m, 1H), 2.52–2.44 (m, 1H), 2.44–2.33 (m, 2H), 2.10–1.97 (m, 2H), 1.75–1.66 (m, 4H), 1.63 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

¹³C-NMR (201 MHz, CDCl₃): δ / ppm = 165.5, 144.0, 140.0, 132.8, 122.5, 60.1, 44.6, 32.0, 31.8, 29.1, 26.0, 18.0, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3418, 2968, 2928, 2858, 1711, 1628, 1588, 1446, 1371, 1345, 1294, 1256, 1238, 1194, 1094, 1049, 1024, 986, 920, 861, 823, 751, 668.

MS (EI, 70 eV): m/z (%) = 208 (M⁺, 39), 162 (28), 139 (73), 111 (72), 93 (34), 69 (100).

HRMS (EI): m/z calc. for [C₁₃H₂₀O₂]⁺: 208.1463; found 208.1459.

(E)-(4,4-dimethylhexa-2,5-dien-1-yl)trimethylsilane (125j)

According to **TP2** prenylzinc bromide in dry THF (0.4 M, 1.86 mL, 0.75 mmol) was added to (*E*)-(3-bromoprop-1-en-1-yl)trimethylsilane (116 mg, 0.6 mmol) in DMPU (1.9 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, pentane) afforded the title compound as a colorless oil (86 mg, 0.47 mmol, 79%).

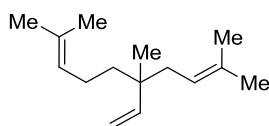
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.96 (dt, J = 18.5, 7.0, 1H), 5.85–5.75 (m, 1H), 5.61 (dt, J = 18.5, 1.3, 1H), 4.92 (s, 1H), 4.88 (d, J = 5.8, 1H), 2.08 (dd, J = 7.0, 1.3, 2H), 0.97 (s, 7H), 0.04 (s, 9H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 148.4, 143.8, 133.2, 110.4, 50.0, 36.9, 26.7, -1.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 690 (m), 705 (m), 748 (m), 767 (w), 834 (vs), 858 (s), 885 (w), 911 (m), 991 (m), 1126 (vw), 1194 (vw), 1247 (m), 1301 (vw), 1363 (w), 1379 (w), 1416 (w), 1470 (vw), 1617 (w), 1640 (w), 2957 (m).

MS (EI, 70 eV): m/z (%) = 182.1 (M⁺, 2), 113.2 (13), 108.1 (24), 73.0 (69), 69.1 (100).

HRMS (EI): m/z calc. for [C₁₁H₂₂Si]⁺: 182.1491; found: 182.1484 (M⁺).

2,5,9-trimethyl-5-vinyldeca-2,8-diene (125k)

According to **TP2** geranylzinc bromide in dry THF (0.31 M, 2.4 mL, 0.75 mmol) was added to 1-bromo-3-methylbut-2-ene (89 mg, 0.6 mmol) in DMPU (2.4 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (103 mg, 0.50 mmol, 83% (94:6:0:0)).

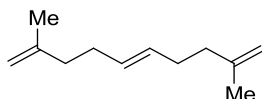
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.73 (dd, J = 17.5, 10.8, 1H), 5.06–5.14 (m, 2H), 4.98 (dd, J = 10.8, 1.5, 1H), 4.90 (dd, J = 17.5, 1.5, 1H), 1.99 (p, J = 7.7, 2H), 1.86 (q, J = 7.7, 2H), 1.71–1.68 (m, 4H), 1.68–1.66 (m, 3H), 1.59 (d, J = 5.2, 6H), 1.32–1.26 (m, 2H), 0.95 (s, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 147.3, 132.9, 131.1, 125.2, 120.9, 111.6, 40.5, 40.4, 39.2, 26.2, 25.9, 23.1, 22.7, 18.1, 17.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 654 (m), 683 (m), 732 (m), 782 (m), 800 (m), 834 (m), 866 (m), 886 (m), 909 (vs), 987 (m), 1001 (s), 1055 (m), 1102 (m), 1133 (m), 1255 (m), 1376 (m), 1413 (m), 1453 (s), 1484 (m), 1549 (m), 1638 (m), 1662 (m), 2857 (m), 2915 (m), 2924 (m), 2967 (m).

MS (EI, 70 eV): m/z (%) = 206.2 (M⁺, 15), 191.2 (17), 163.1 (51), 137.1 (100), 95.1 (92), 82.1 (57), 69.2 (48).

HRMS (EI): m/z calc. for [C₁₅H₂₆]⁺: 206.2035; found: 206.2026 (M⁺).

(E)-2,9-Dimethyldeca-1,5,9-triene (125l)

According to **TP2** (2-methylallyl)zinc bromide in dry THF (0.30 M, 4.00 mL, 1.20 mmol) was added to (E)-1,4-dibromobut-2-ene (107 mg, 0.50 mmol) in DMPU (4.00 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 20:1) afforded the title compound as a colorless oil (74 mg, 0.45 mmol, 90%).

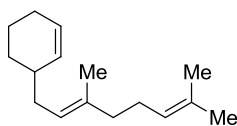
¹H-NMR (800 MHz, CDCl₃): δ / ppm = 5.47–5.39 (m, 2H), 4.73–4.63 (m, 4H), 2.19–2.09 (m, 4H), 2.09–2.01 (m, 4H), 1.75–1.68 (m, 6H).

¹³C-NMR (201 MHz, CDCl₃): δ / ppm = 145.8, 130.1, 110.0, 77.5, 77.2, 76.8, 38.0, 30.9, 22.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2956 (m), 2924 (m), 2854 (m), 1740 (m), 1716 (m), 1458 (m), 1377 (m), 1261 (m), 1092 (m), 1022 (m), 799 (m).

MS (EI, 70 eV): m/z (%) = 164 (M⁺, 1), 149 (51), 135 (7), 122 (10), 108 (30), 93 (50), 81 (54), 67 (100), 55 (64).

HRMS (EI): m/z calc. for [C₁₁H₁₇]⁺: 149.1330; found 149.1335 (M–Me).

(E)-3-(3,7-dimethylocta-2,6-dien-1-yl)cyclohex-1-ene (125m)

According to **TP2** cyclohex-2-en-1-ylzinc bromide in dry THF (0.24 M, 2.5 mL, 0.6 mmol) was added to (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (104 mg, 0.48 mmol) in DMPU (2.5 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (78 mg, 0.36 mmol, 74%).

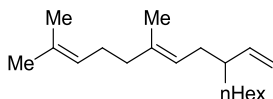
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.69–5.64 (m, 1H), 5.60–5.56 (m, 1H), 5.21–5.13 (m, 1H), 5.12–5.07 (m, 1H), 2.14–2.05 (m, 3H), 2.04–1.93 (m, 6H), 1.80–1.69 (m, 2H), 1.68 (d, J = 1.4, 3H), 1.60 (d, J = 3.1, 6H), 1.57–1.45 (m, 2H), 1.29–1.16 (m, 1H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 136.0, 132.2, 131.4, 127.0, 124.5, 123.2, 40.0, 36.1, 34.7, 29.1, 26.8, 25.9, 25.5, 21.7, 17.8, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 558 (m), 567 (w), 591 (w), 604 (w), 675 (s), 700 (m), 720 (vs), 835 (m), 859 (m), 887 (m), 956 (w), 1108 (w), 1376 (m), 1436 (m), 1446 (s), 2839 (m), 2856 (s), 2922 (vs), 2966 (m), 3017 (w).

MS (EI, 70 eV): m/z (%) = 218.2 (M⁺, 6), 137.0 (14), 95.0 (16), 81.1 (100), 69.1 (52), 40.7 (10).

HRMS (EI): m/z calc. for [C₁₆H₂₆]⁺: 218.2035; found: 218.2026 (M⁺).

(Z)-2,6-Dimethyl-9-vinylpentadeca-2,6-diene (125n)

According to **TP2** (*E*)-non-2-en-1-ylzinc bromide in dry THF (0.30 M, 2.00 mL, 0.60 mmol) was added to geranyl bromide (109 mg, 0.50 mmol) in DMPU (0.5 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane) afforded the title compound as a colorless oil (110 mg, 0.42 mmol, 84%).

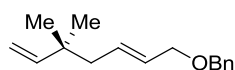
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.66–5.51 (m, 1H), 5.18–5.01 (m, 2H), 4.99–4.85 (m, 2H), 2.15–1.88 (m, 7H), 1.71–1.63 (m, 3H), 1.63–1.54 (m, 5H), 1.44–1.07 (m, 10H), 0.86 (t, J = 6.7 Hz, 2H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 143.5, 135.7, 131.3, 124.6, 122.9, 113.8, 44.5, 40.0, 34.4, 33.6, 32.0, 29.6, 27.3, 26.9, 25.8, 22.8, 17.8, 16.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3423, 2955, 2927, 2872, 2857, 1717, 1641, 1457, 1418, 1378, 1165, 1071, 995, 951, 912, 725, 668.

MS (EI, 70 eV): m/z (%) = 262 (M⁺, 1), 247 (2), 219 (4), 95 (14), 81 (38), 69 (100), 55 (28).

HRMS (EI): m/z calc. for [C₁₉H₃₄]: 262.2661; found: 262.2657 (M⁺).

(E)-(((5,5-Dimethylhepta-2,6-dien-1-yl)oxy)methyl)benzene ((E)- γ,α' -125o)

According to **TP2** prenylzinc bromide in dry THF (0.44 M, 1.5 mL, 0.66 mmol) was added to (E)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene (130 mg, 0.54 mmol) in DMPU (1.5 mL) and the mixture was stirred for 24 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane:ether 20:1) afforded the title compound as a colorless oil (96 mg, 0.42 mmol, 77%).

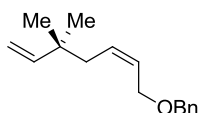
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ / ppm = 7.34 (m, 4H), 7.30 (m, 1H), 5.86–5.76 (m, 1H), 5.72–5.52 (m, 2H), 4.94 (s, 1H), 4.90 (dd, J = 6.2, 1.3, 1H), 4.50 (s, 2H), 3.98 (d, J = 6.0, 2H), 2.06 (d, J = 6.0, 2H), 1.00 (s, 6H).

$^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ / ppm = 148.2, 138.5, 131.6, 128.9, 128.5, 127.9, 127.7, 110.6, 71.8, 70.9, 45.5, 36.9, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 696 (vs), 733 (s), 818 (w), 910 (s), 972 (s), 1000 (m), 1028 (m), 1061 (m), 1107 (s), 1156 (w), 1202 (w), 1362 (m), 1379 (w), 1414 (w), 1454 (m), 1470 (w), 1496 (w), 1639 (w), 2853 (w), 2927 (w), 2961 (w).

MS (EI, 70 eV): m/z (%) = 230.2 (M^+ , 1), 108.0 (11), 107.0 (10), 92.0 (13), 91.0 (100), 69.1 (89).

HRMS (EI): m/z calc. for $[\text{C}_{16}\text{H}_{22}\text{O}]$: 230.1671; found: 230.1654 (M^+).

(Z)-(((5,5-dimethylhepta-2,6-dien-1-yl)oxy)methyl)benzene ((Z)- γ,α' -125o)

According to **TP2** prenylzinc bromide in dry THF (0.4 M, 1.86 mL, 0.75 mmol) was added to (Z)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene (145 mg, 0.6 mmol) in DMPU (1.9 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane:ether 20:1) afforded the title compound as a colorless oil (105 mg, 0.46 mmol, 76%).

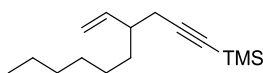
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ / ppm = 7.37–7.27 (m, 4H), 5.83–5.72 (m, 1H), 5.73–5.65 (m, 1H), 5.63–5.55 (m, 1H), 4.94 (s, 1H), 4.93–4.87 (m, 1H), 4.51 (s, 2H), 4.07 (dd, J = 6.4, 1.3, 2H), 2.04 (dd, J = 7.6, 1.3, 2H), 0.99 (s, 6H).

$^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ / ppm = 147.9, 138.5, 130.2, 128.5, 127.9, 127.9, 127.7, 110.8, 72.3, 66.0, 40.2, 37.1, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 696 (vs), 712 (s), 736 (s), 828 (m), 876 (m), 911 (s), 999 (s), 1027 (m), 1070 (s), 1097 (s), 1176 (w), 1203 (m), 1272 (m), 1313 (w), 1344 (w), 1363 (m), 1380 (m), 1414 (w), 1454 (m), 1470 (w), 1496 (w), 1641 (w), 1704 (w), 1722 (w), 2868 (w), 2961 (m), 3030 (w).

MS (EI, 70 eV): m/z (%) = 229.2 (0.3), 108.8 (13), 107.7 (12), 92.0 (13).

HRMS (EI): m/z calc. for $[\text{C}_{16}\text{H}_{21}\text{O}]^+$: 229.1568; found: 229.1592 ($\text{M} - \text{H}^+$).

Trimethyl(4-vinyldec-1-yn-1-yl)silane (127a)

According to **TP2** (*E*)-oct-2-en-1-ylzinc bromide in dry THF (0.24 M, 2.76 mL, 0.66 mmol) was added to (3-chloroprop-1-yn-1-yl)trimethylsilane (81 mg, 0.55 mmol) in DMPU (2.75 mL) and the mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 80:1) afforded the title compound as a colorless oil (114 mg, 0.48 mmol, 88%).

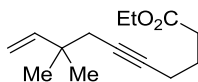
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.74–5.60 (m, 1H), 5.08–4.96 (m, 2H), 2.27–2.23 (m, 2H), 2.22–2.13 (m, 1H), 1.36–1.19 (m, 8H), 0.92–0.83 (m, 3H), 0.14 (s, 9H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 141.6, 114.8, 106.0, 85.9, 42.9, 33.7, 31.9, 29.4, 27.0, 25.9, 22.8, 14.2, 0.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2923, 2361, 2340, 1734, 1559, 1458, 668.

MS (EI, 70 eV): m/z (%) = 236 (M⁺, 1), 221 (2), 165 (9), 152 (8), 128 (20), 85 (18), 73 (100).

HRMS (EI): m/z calc. for [C₁₄H₂₅Si]⁺: 221.1726; found 221.1726 (M–Me).

Ethyl 8,8-Dimethyldec-9-en-5-ynoate (127b)

According to **TP2** prenylzinc bromide in dry THF (0.36 M, 2.1 mL, 0.75 mmol) was added to ethyl 7-bromohept-5-ynoate (140 mg, 0.6 mmol) in DMPU (2.1 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 25:1) afforded the title compound as a colorless oil (106 mg, 0.48 mmol, 79%).

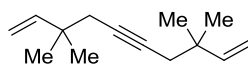
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.87 (dd, J = 17.5, 10.7, 1H), 5.01–4.91 (m, 2H), 4.13 (q, J = 7.1, 2H), 2.43 (t, J = 7.5, 2H), 2.24 (tt, J = 6.9, 2.4, 2H), 2.12 (t, J = 2.4, 2H), 1.85–1.75 (m, 2H), 1.26 (t, J = 7.1, 4H), 1.07 (s, 6H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 173.5, 147.3, 110.9, 80.9, 78.8, 60.4, 36.8, 33.3, 32.6, 26.5, 24.5, 18.4, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 683 (w), 805 (w), 868 (w), 912 (m), 999 (w), 1008 (w), 1028 (m), 1054 (m), 1097 (w), 1115 (w), 1156 (s), 1176 (m), 1207 (m), 1243 (m), 1311 (w), 1323 (w), 1364 (w), 1375 (m), 1416 (w), 1464 (w), 1641 (w), 1734 (vs), 2873 (w), 2909 (w), 2934 (w), 2963 (w).

MS (EI, 70 eV): m/z (%) = 222 (M⁺, 0.4), 207 (19), 177 (10), 161 (10), 134 (20), 121 (23), 69 (100).

HRMS (EI): m/z calc. for [C₁₄H₂₂O₂]⁺: 222.1620; found 222.1614 (M⁺).

3,3,8,8-Tetramethyldeca-1,9-dien-5-yne (127c)

According to **TP2** prenylzinc bromide in dry THF (0.36 M, 6.94 mL, 2.50 mmol) was added to 1,4-dibromobut-2-yne (212 mg, 1.00 mmol) in DMPU (7 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohehexane) afforded the title compound as a colorless oil (162 mg, 0.85 mmol, 85%).

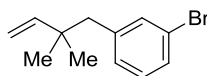
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 5.82 (dd, J = 17.5, 10.7 Hz, 2H), 4.96–4.82 (m, 4H), 2.08 (s, 4H), 1.02 (s, 12H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 147.5, 110.8, 79.6, 37.0, 32.7, 26.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3084, 3002, 2962, 2928, 2908, 2870, 2832, 1642, 1468, 1416, 1380, 1362, 1318, 1262, 1194, 1180, 1142, 1048, 998, 910, 872, 806, 722, 686.

MS (EI, 70 eV): m/z (%) = 190 (M⁺, 1), 175 (18), 147 (20), 119 (13), 105 (14), 91 (11), 79 (8), 69 (100), 53 (8).

HRMS (EI): m/z calc. for [C₁₃H₁₉]⁺: 175.1487; found: 175.1496 ([M–Me]⁺).

1-Bromo-3-(2,2-dimethylbut-3-en-1-yl)benzene (129a)

According to **TP2** prenylzinc bromide in dry THF (0.36 M, 1.67 mL, 0.6 mmol) was added to 1-bromo-3-(bromomethyl)benzene (125 mg, 0.50 mmol) in DMPU (1.7 mL) and the mixture was stirred for 1 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohehexane) afforded the title compound as a colorless oil (75 mg, 0.31 mmol, 63%).

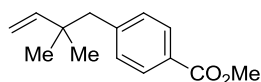
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.31–7.23 (m, 1H), 7.23–7.17 (m, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.97 (dt, J = 7.7, 1.3 Hz, 1H), 5.76 (dd, J = 17.5, 10.7 Hz, 1H), 4.87 (dd, J = 10.7, 1.3 Hz, 1H), 4.79 (dd, J = 17.5, 1.3 Hz, 1H), 2.48 (s, 2H), 0.94 (s, 6H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 147.6, 141.3, 133.5, 129.3, 129.2, 129.2, 121.8, 111.2, 48.8, 37.8, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3083, 2961, 2927, 2869, 2361, 2340, 1639, 1593, 1566, 1472, 1425, 1362, 1206, 1072, 998, 912, 886, 844, 782, 726, 697, 668.

MS (EI, 70 eV): m/z (%) = 238 (M⁺, 8), 171 (10), 115 (7), 90 (9), 69 (100).

HRMS (EI): m/z calc. for [C₁₂H₁₅Br]⁺: 238.0357; found: 238.0346 (M⁺).

Methyl 4-(2,2-Dimethylbut-3-en-1-yl)benzoate (129b)

According to a modified **TP2** prenylzinc bromide in dry THF (0.36 M, 1.39 mL, 0.5 mmol) was added to methyl 4-(bromomethyl)benzoate (115 mg, 0.50 mmol) in DMPU (1.4 mL) and the mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/ether 20:1) afforded the title compound as a colorless oil (78 mg, 0.36 mmol, 72%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.92 (d, J = 8.2, 2H), 7.17 (d, J = 8.2, 2H), 5.83 (dd, J = 17.4, 10.7, 1H), 4.92 (dd, J = 10.7, 1.2, 1H), 4.82 (dd, J = 17.4, 1.2, 1H), 3.90 (s, 3H), 2.63 (s, 2H), 1.00 (s, 6H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 167.4, 147.6, 144.6, 130.7, 129.0, 128.0, 111.2, 52.1, 49.2, 38.0, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 684 (w), 702 (m), 722 (s), 772 (m), 804 (w), 836 (w), 860 (m), 912 (m), 970 (w), 1006 (w), 1020 (m), 1100 (s), 1110 (s), 1178 (s), 1274 (vs), 1310 (w), 1364 (w), 1380 (w), 1416 (m), 1434 (m), 1462 (w), 1574 (vw), 1612 (m), 1638 (w), 1720 (vs), 2870 (vw), 2928 (w), 2960 (w), 3084 (vw).

MS (EI, 70 eV): m/z (%) = 218 (M⁺, 0.4), 187 (8), 150 (100), 90 (6), 69 (20).

HRMS (EI): m/z calc. for [C₁₄H₁₈O₂]⁺: 218.1307; found: 218.1304 (M⁺).

6 Preparation of Tertiary Amines by the Reaction of Iminium Ions Derived from Unsymmetrical Aminals with Zinc and Magnesium Organometallics

MeLi was purchased as a solution in diethylether from Rockwood Lithium GmbH and the content of organometallic reagent was determined by the method of Paquette using *i*PrOH and 1,10-phenanthroline as indicator.¹⁴⁵ MeMgCl was purchased as a solution in THF from Rockwood Lithium GmbH and titrated against iodine prior to use. Following compounds were prepared according to literature procedures: **136a**, **137a**, **138a,b** and titrated against iodine prior to use.¹⁴⁶

Procedure A

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N,N,N',N'*-tetramethylmethanediamine (**2**, 1.0 equiv) and anhydrous CH₂Cl₂ to obtain a 1 M

¹⁴⁵ H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, 24, 2503.

¹⁴⁶ F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, 15, 7192.

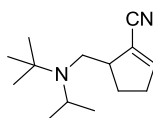
solution. After cooling to 0 °C, trifluoroacetic anhydride (1.0 equiv) was added dropwise and the solution was allowed to stir for 15 min at 0 °C. A second dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding amine (1.0 equiv) and THF to obtain a 0.2 M solution. After cooling to 0 °C, MeMgCl (1.1 equiv. 3.1 M in THF) was added dropwise and the solution was stirred for 30 min. Next, the magnesium amide was added over 15 min to the previously prepared methylene(dimethyl)iminium trifluoroacetate (**1**) at 0 °C and stirring was continued for another 30 min. After, trifluoroacetic anhydride (1.0 equiv) was added, resulting in the formation of a white precipitate and the mixture was stirred for 15 min. Finally, the desired organomagnesium / organozinc reagent (1.1 equiv) was added at –78 °C and the reaction mixture warmed to room temperature giving a clear solution. The crude mixture was quenched with sat. aq. NaHCO₃ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aq. NaCl and the solvent was removed *in vacuo*.

Procedure B

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N,N,N',N'*-tetramethylmethanediamine (**2**, 1.0 equiv) and anhydrous CH₂Cl₂ to obtain a 1 M solution. After cooling to 0 °C, trifluoroacetic anhydride (1.0 equiv) was added dropwise and the solution was allowed to stir for 15 min at 0 °C.

A second dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding amine (1.0 equiv) and THF to obtain a 0.2 M solution. After cooling to –78 °C, MeLi (1.1 equiv., 1.6 M in Et₂O) was added dropwise and the solution was stirred for 30 min. Next, the lithium amide was added over 15 min to the previously prepared methylene(dimethyl)iminium trifluoroacetate (**1**) –78 °C and stirring was continued for another 30 min. Then, trifluoroacetic anhydride (1.0 equiv) was added, resulting in the formation of a white precipitate and the mixture was stirred for 15 min. Finally, the desired organomagnesium / organozinc reagent (1.1 equiv) was added at –78 °C and the reaction mixture warmed to room temperature giving a clear solution. The crude mixture was quenched with sat. aq. NaHCO₃ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aq. NaCl and the solvent was removed *in vacuo*.

5-((*tert*-Butyl(isopropyl)amino)methyl)cyclopent-1-enecarbonitrile (**139a**)



Prepared according to **Procedure B** from *N*-isopropyl-2-methylpropan-2-amine (**133a**, 1.2 mmol, 135 mg, 1.2 equiv) and (2-cyanocyclopent-2-en-1-yl)zinc chloride (**123g**, 3.16 mL, 0.38 M in THF, 1.2 mmol, 1.2equiv). Purification of the crude product by flash chromatography (Al₂O₃,

isohexane/EtOAc = 20:1) afforded 5-((*tert*-butyl(isopropyl)amino)methyl)cyclopent-1-enecarbonitrile as a colorless liquid (185 mg, 0.84 mmol, 84%).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 6.66–6.57 (m, 1H), 3.27 (p, J = 7.0 Hz, 1H), 3.00–2.93 (m, 1H), 2.68 (dd, J = 14.3, 7.1 Hz, 1H), 2.51–2.35 (m, 3H), 2.10–1.91 (m, 1H), 1.85–1.69 (m, 1H), 1.07 (s, 9H), 0.99 (dd, J = 13.1, 6.7 Hz, 6H).

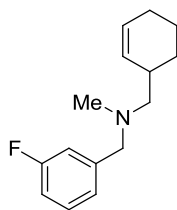
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 149.2, 119.4, 117.5, 55.9, 49.2, 46.7, 32.3, 28.7, 27.9, 23.3, 22.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2971, 2872, 2845, 2217, 1611, 1466, 1436, 1392, 1362, 1278, 1247, 1204, 1160, 1112, 1062, 1054, 1016, 999, 956, 906, 862, 848, 785, 717, 668.

MS (EI, 70 eV): m/z (%) = 205 (M-CH₃, 4), 163 (11), 149 (8), 128 (53), 106 (4), 92 (5), 72 (100), 57 (19).

HRMS (EI): m/z calc. for [C₁₃H₂₁N₂⁺]: 205.1705; found: 205.1686 (M-CH₃).

1-(Cyclohex-2-en-1-yl)-*N*-(3-fluorobenzyl)-*N*-methylethanamine (139b)



Prepared according to **Procedure B** from 1-(3-fluorophenyl)-*N*-methylethanamine (**133b**, 1.0 mmol, 153 mg, 1.1 equiv) and cyclohex-2-en-1-ylzinc bromide (**123i**, 4.00 mL, 0.30 M in THF, 1.2 mmol, 1.2equiv). Purification of the crude product by flash chromatography (SiO₂, isohexane + 2% TEA) afforded 1-(cyclohex-2-en-1-yl)-*N*-(3-fluorobenzyl)-*N*-methylethanamine as a colorless liquid (177 mg, 0.76 mmol, 76%).

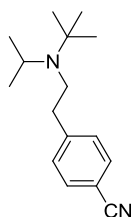
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.28–7.18 (m, 1H), 7.11–7.01 (m, 2H), 6.95–6.85 (m, 1H), 5.74–5.61 (m, 2H), 3.53–3.38 (m, 2H), 2.36–2.26 (m, 1H), 2.26–2.20 (m, 2H), 2.17 (s, 3H), 2.04–1.89 (m, 2H), 1.88–1.74 (m, 1H), 1.72–1.59 (m, 1H), 1.58–1.43 (m, 1H), 1.38–1.20 (m, 1H).

¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 163.10 (d, J = 245.0 Hz), 142.64 (d, J = 7.0 Hz), 130.24, 129.62 (d, J = 8.2 Hz), 127.79, 124.41 (d, J = 2.8 Hz), 115.64 (d, J = 21.3 Hz), 113.78 (d, J = 21.3 Hz), 63.48, 62.32 (d, J = 1.9 Hz), 42.69, 33.57, 27.62, 25.70, 21.27.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3019, 2926, 2838, 2786, 1616, 1589, 1486, 1447, 1364, 1348, 1319, 1272, 1254, 1151, 1128, 1091, 1072, 1050, 1028, 944, 926, 880, 864, 845, 781, 749, 722, 684.

MS (EI, 70 eV): m/z (%) = 232 (M-H, 1), 152 (100), 136 (2), 109 (99), 96 (2), 83 (11), 67 (3).

HRMS (EI): m/z calc. for [C₁₅H₁₉FN⁺]: 232.1502; found: 232.1508 (M-H).

4-(2-(*tert*-Butyl(isopropyl)amino)ethyl)benzonitrile (139c)

Prepared according to **Procedure B** from *N*-isopropyl-2-methylpropan-2-amine (133a, 1.0 mmol, 115 mg, 1.0 equiv) and (4-cyanobenzyl)zinc chloride (136a, 1.25 mL, 0.8 M in THF, 1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, isohexane/EtOAc = 5:1 + 2% TEA) afforded 4-(2-(*tert*-butyl(*isopropyl*)amino)ethyl)benzonitrile as a yellow oil (176 mg, 0.72 mmol, 72%).

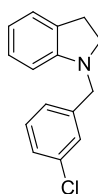
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.55 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 3.38 (hept, J = 6.6 Hz, 1H), 2.80–2.60 (m, 4H), 1.11 (s, 9H), 1.00 (d, J = 6.6 Hz, 6H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 147.2, 132.3, 129.6, 119.3, 109.8, 55.6, 46.9, 44.7, 42.4, 29.2, 22.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2971, 2872, 2228, 1608, 1504, 1476, 1468, 1414, 1391, 1378, 1361, 1260, 1229, 1187, 1176, 1158, 1110, 1048, 1018, 964, 864, 848, 822.

MS (EI, 70 eV): m/z (%) = 229 (M-CH₃⁺, 13), 187 (15), 173 (12), 128 (67), 116 (9), 103 (8), 89 (6), 72 (100).

HRMS (EI): m/z calc. for C₁₅H₂₁N₂⁺ (229.1705, M⁺-CH₃); found: 229.1699.

1-(3-Chlorobenzyl)indoline (139d)

Prepared according to Procedure B from indoline (133c, 1.0 mmol, 119 mg, 1.0 equiv) and (3-chlorophenyl)zinc iodide (137a, 2.33 mL, 0.43 M in THF, 1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (Al₂O₃, isohexane/EtOAc = 100:1) afforded 1-(3-chlorobenzyl)indoline as a colorless oil (160 mg, 0.66 mmol, 66%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.40–7.32 (m, 1H), 7.28–7.17 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 7.06–7.01 (m, 1H), 6.73–6.60 (m, 1H), 6.45 (d, J = 7.8 Hz, 1H), 4.20 (s, 2H), 3.31 (t, J = 8.3 Hz, 2H), 2.97 (t, J = 8.2 Hz, 2H).

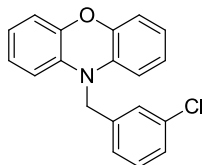
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 152.4, 140.9, 134.6, 130.1, 129.9, 128.0, 127.5, 127.5, 126.0, 124.7, 118.2, 107.2, 54.0, 53.6, 28.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3049, 2921, 2821, 1701, 1606, 1597, 1575, 1486, 1472, 1430, 1378, 1343, 1304, 1264, 1225, 1196, 1155, 1146, 1075, 1052, 1020, 980, 943, 862, 778, 741, 682.

MS (EI, 70 eV): m/z (%) = 243 (M^+ , 100), 207 (7), 132 (54), 118 (52), 103 (11), 91 (29), 77 (11), 65 (14).

HRMS (EI): m/z calc. for $[C_{15}H_{14}ClN]$: 243.0815; found: 243.0809 (M^+).

10-(3-chlorobenzyl)-10*H*-phenoxazine (**139e**)



Prepared according to Procedure A from 10*H*-phenoxazine (**133d**, 183 mg, 1.0 mmol, 1.0 equiv) and 3-chlorophenylmagnesium chloride (**138a**, 2.75 mL, 0.40 M in THF, 1.1 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3 , *isohexane*/EtOAc = 99:1) afforded **139e** as a yellow oil (246 mg, 80%).

Mp.: 114.8–115.9 °C

1H -NMR (300 MHz, $CDCl_3$) δ /ppm = 7.21–7.09 (m, 4H), 6.62–6.57 (m, 6H), 6.20 (d, J = 6.83 Hz, 2H), 4.65 (s, 2H).

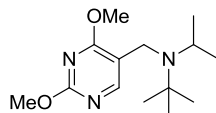
^{13}C -NMR (75 MHz, $CDCl_3$) δ /ppm = 145.1, 138.8, 134.9, 133.5, 130.2, 127.5, 126.1, 124.1, 123.7, 121.5, 115.4, 112.1, 49.1.

IR (cm^{-1}): $\tilde{\nu}$ = 3070, 3056, 3025, 2943, 2924, 2888, 2854, 1628, 1591, 1578, 1488, 1475, 1463, 1428, 1378, 1325, 1313, 1294, 1272, 1253, 1200, 1186, 1130, 1082, 1051, 1004, 910, 867, 850, 825, 768, 727, 708, 678.

MS (70 eV, EI) m/z (%) = 307 (11) [M^+], 183 (14), 182 (100), 127 (5).

HRMS for $C_{19}H_{14}^{35}ClNO$ (307.0764): found: 307.0757.

N-((2,4-Dimethoxypyrimidin-5-yl)methyl)-*N*-isopropyl-2-methylpropan-2-amine (**139f**)



Prepared according to **Procedure B** from *N*-isopropyl-2-methylpropan-2-amine (**133a**, 1.0 mmol, 97 mg, 1.0 equiv) and (2,4-dimethoxypyrimidin-5-yl)magnesium bromide (**138b**, 0.83 mL, 1.2 M in THF, 1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2 , *isohexane*/EtOAc = 20:1 + 2% TEA) afforded *N*-((2,4-dimethoxypyrimidin-5-yl)methyl)-*N*-isopropyl-2-methylpropan-2-amine as a yellow oil (164 mg, 0.61 mmol, 61%).

1H -NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (t, J = 1.2 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.60 (d, J = 1.2 Hz, 2H), 3.55–3.42 (m, 1H), 1.07 (s, 9H), 0.98 (d, J = 6.6 Hz, 6H).

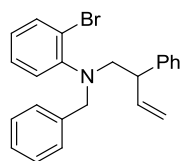
^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 168.0, 163.9, 157.7, 118.5, 55.6, 54.6, 53.8, 47.0, 37.6, 28.8, 22.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2872, 1600, 1571, 1458, 1375, 1315, 1292, 1264, 1253, 1234, 1195, 1173, 1154, 1097, 1074, 1054, 1041, 1017, 972, 936, 788, 756.

MS (EI, 70 eV): m/z (%) = 267 (M^+ , 7), 252 (32), 196(3), 153 (100), 123 (6).

HRMS (EI): m/z calc. for $[\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_2]$: 267.1947; found: 267.1928 (M^+).

***N*-Benzyl-2-bromo-*N*-(2-phenylbut-3-en-1-yl)aniline (139g)**



Prepared according to **Procedure B** from *N*-benzyl-2-bromoaniline (**133e**, 1.0 mmol, 262 mg, 1.0 equiv) and cinnamylzinc chloride (**123c**, 2.86 mL, 0.35 M in THF, 1.0 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2 , isohexane/EtOAc = 100:1 + 2% TEA) afforded the racemic *N*-benzyl-2-bromo-*N*-(2-phenylbut-3-en-1-yl)aniline as a colorless oil (278 mg, 0.71 mmol, 71%).

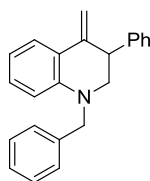
^1H -NMR (600 MHz, CDCl_3): δ / ppm = 7.59 (dd, J = 7.9, 1.5 Hz, 1H), 7.35–7.15 (m, 9H), 7.07–6.97 (m, 3H), 6.93 (td, J = 7.6, 1.5 Hz, 1H), 5.98 (ddd, J = 17.3, 10.3, 7.2 Hz, 1H), 5.05–5.00 (m, 1H), 4.90 (d, J = 17.2 Hz, 1H), 4.14 (s, 2H), 3.44 (q, J = 7.5 Hz, 1H), 3.38–3.31 (m, 1H), 3.31–3.24 (m, 1H).

^{13}C -NMR (151 MHz, CDCl_3): δ / ppm = 148.9, 142.6, 140.2, 138.2, 134.2, 128.9, 128.4, 128.2, 128.2, 127.7, 127.2, 126.5, 124.9, 124.8, 122.0, 115.5, 59.5, 56.0, 47.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3027, 2921, 2824, 1637, 1601, 1584, 1494, 1473, 1452, 1436, 1417, 1363, 1291, 1267, 1205, 1146, 1113, 1075, 1027, 992, 955, 914, 844, 753, 722, 696, 658.

MS (ESI, 70 eV): m/z (%) = 391 (M^+ , 1), 274 (50), 194 (8), 178 (4), 154 (6), 115 (9), 91 (100).

HRMS (EI): m/z calc. for $[\text{C}_{23}\text{H}_{23}\text{BrN}^+]$: 392.1008; found: 392.10073 ($\text{M}+\text{H}^+$).

1-Benzyl-4-methylene-3-phenyl-1,2,3,4-tetrahydroquinoline (140)¹⁴⁷

To *N*-benzyl-2-bromo-*N*-(2-phenylbut-3-en-1-yl)aniline (**139g**, 100 mg, 0.25 mmol) in dry toluene (0.5 mL) was added triethylamine (56 mg, 0.55 mmol) and tetrakis(triphenylphosphine)palladium(0) (29 mg, 25 μ mol, 10 mol%) and the mixture was stirred 48 h at 70 °C. Then sat. aq. NH_4Cl (0.5 mL) was added and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic phases were dried (MgSO_4). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *n*hexane / EtOAc = 80:1 + 2% TEA) afforded the title compound (**140**, 69 mg, 0.22 mmol, 89%) as a colorless solid.

Mp.: 114–116 °C.

^1H -NMR (300 MHz, CDCl_3): δ / ppm = 7.62 (dd, J = 7.8, 1.6 Hz, 1H), 7.41–7.02 (m, 11H), 6.75–6.54 (m, 2H), 5.62–5.54 (m, 1H), 4.68–4.61 (m, 1H), 4.48 (s, 2H), 3.95–3.84 (m, 1H), 3.70–3.56 (m, 2H).

^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 145.2, 143.9, 141.7, 138.5, 129.5, 128.7, 128.5, 128.4, 127.0, 126.8, 126.8, 125.5, 121.5, 116.9, 112.4, 107.7, 55.9, 55.8, 46.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3085, 3060, 3028, 2923, 2860, 2360, 1624, 1598, 1584, 1563, 1493, 1476, 1450, 1410, 1351, 1317, 1297, 1269, 1243, 1222, 1194, 1170, 1162, 1120, 1080, 1055, 1030, 1006, 1001, 961, 940, 888, 836, 816, 750, 730, 711, 703, 694.

MS (EI, 70 eV): m/z (%) = 311 (M^+ , 100), 296 (3), 282 (3), 234 (11), 220 (36), 204 (14), 115 (10), 91 (44).

HRMS (EI): m/z calc. for $[\text{C}_{23}\text{H}_{21}\text{N}]$: 311.1674; found: 311.1674 (M^+).

¹⁴⁷ U. Martínez-Estíbalez, O. García-Calvo, V. Ortiz-de-Elguea, N. Sotomayor, E. Lete, *Eur. J. Org. Chem.* **2013**, 15, 3013.

7 Synthesis of Novel Ephedrine Derivatives Containing a Tertiary Amine

Compounds **136d-f** were prepared according to literature procedures and titrated against iodine prior to use.¹⁴⁸

7.1 Preparation of (1*S*,2*R*)/(1*R*,2*S*)-*O*-(*tert*-Butyldimethylsilyl)ephedrine¹⁴⁹



To (+ or -)-ephedrine (hydrochloride salt, 1.01 g, 5.00 mmol) in dry DMF (15 mL) was added imidazole (0.68 g, 10.0 mmol) and *tert*-butylchlorodimethylsilane (1.06 g, 7 mmol) and the mixture was stirred for 24 h at 70 °C. Then sat. aq. NaHCO₃ (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (MgSO₄). Evaporation of the solvents *in vacuo* and purification by flash column chromatography (silica gel, *n*hexane / EtOAc = 20:1 + 2% TEA) afforded the title compound (840 mg, 3.01 mmol, 60%) as a colorless oil.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.37–7.17 (m, 5H), 4.60 (d, *J* = 5.0 Hz, 1H), 2.72–2.57 (m, 1H), 2.37 (s, 3H), 1.28 (s, br, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), -0.20 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 143.1, 128.1, 127.3, 127.0, 77.5, 61.8, 34.2, 26.0, 25.9, 18.3, 14.8, -4.4, -4.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2956, 2930, 2885, 2857, 2791, 1472, 1463, 1453, 1389, 1376, 1361, 1253, 1202, 1189, 1158, 1134, 1098, 1060, 1006, 938, 910, 867, 833, 774, 733, 700, 671.

MS (EI, 70 eV): *m/z* (%) = 222 (5), 191 (2), 163 (4), 149 (5), 133 (2), 117 (3), 88 (5), 73 (12), 58 (100).

HRMS (EI): *m/z* calc. for [C₁₆H₃₀NOSi⁺]: 280.2091; found: 280.0276 (M+H).

7.2 Typical Procedures

Typical Procedure for the Preparation of the Benzylzinc Halides of Type 136 (TP1):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with LiCl (466 mg, 11.0 mmol). The flask was heated to 450 °C for 10 min under high vacuum followed by the addition of zinc dust (1.31 g, 20.0 mmol). The vessel was evacuated and refilled with argon. THF (10 mL) and 1,2-dibromoethane (215 μ L, 2.50 mmol) were added via syringe and the reaction mixture

¹⁴⁸ F. M. Piller, A Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

¹⁴⁹ C. Fotsch, J. D. Sonnenberg, N. Chen, C. Hale, W. Karbon, M. H. Norman, *J. Med. Chem.* **2001**, *44*, 2344.

was heated to 50 °C until bubbling occurred. The benzylic halide (10.0 mmol) was added dropwise as a solution in THF (10 mL) over a period of 15 min. The mixture was stirred for the given time at room temperature before the zinc powder was allowed to settle down. The supernatant solution was carefully filtrated using a syringe filter and the yield of the resulting solution of the benzylzinc halide was determined by iodometric titration.

Typical Procedure for the Preparation of Tertiary Ephedrine Derivatives (TP2):

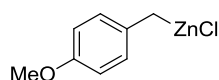
A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N,N,N',N'*-tetramethylmethanediamine (1.0 equiv) and anhydrous CH_2Cl_2 to obtain a 1 M solution. After cooling to $-20\text{ }^\circ\text{C}$, trifluoroacetic anhydride (1.0 equiv) was added dropwise and the solution was allowed to stir for 15 min at $-20\text{ }^\circ\text{C}$. A second dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the TBS-protected ephedrine derivative (1.1 equiv) and THF to obtain a 0.2 M solution. After cooling to $-20\text{ }^\circ\text{C}$, MeMgCl (1.1 equiv., 2.8 M in THF) was added dropwise and the solution was stirred for 30 min. Next, the magnesium amide was added over 15 min to the previously prepared methylene(dimethyl)iminium trifluoroacetate at $-20\text{ }^\circ\text{C}$ and stirring was continued for another 30 min. Then, trifluoroacetic anhydride (1.0 equiv) was added, resulting in the formation of a white precipitate. The mixture was stirred for 15 min before the desired organomagnesium/organozinc reagent (1.1 equiv) was added at $-78\text{ }^\circ\text{C}$ and the reaction mixture warmed to room temperature giving a clear solution. Sat. aq. NaHCO_3 was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with MgSO_4 , the solvent was removed *in vacuo* and purification by column chromatography afforded the expected products.

Typical Procedure for the Deprotection of Tertiary Ephedrine Derivatives Prepared with TP4 (TP3):

A round bottom flask, equipped with a magnetic stirring bar and a septum, was charged with the tertiary ephedrine derivative (1.0 equiv), 5 mL dry CH_2Cl_2 and TBAF· $3\text{H}_2\text{O}$ (4.0 equiv). The progress of the reaction was monitored by GC-analysis of the consumption of the starting material. Upon complete deprotection after 12 h, 5 mL sat. aq. NaHCO_3 solution was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with MgSO_4 , the solvent was removed *in vacuo* and purification by column chromatography afforded the expected products.

7.3 Preparation of Benzylic Organozinc Reagents

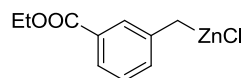
(4-Methoxybenzyl)zinc Chloride (136b)



According to TP2 1-(chloromethyl)-4-methoxybenzene (**136b**) (0.783 g, 5.00 mmol) in THF (3 mL) was added to a mixture of activated zinc powder (0.653 g, 10.0 mmol), LiCl (0.266 g, 7.50 mmol) and

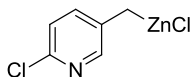
THF (5 mL). After 12 h at 25 °C the reaction was finished and iodometric titration indicates a concentration of 0.56 M, which corresponds to a yield of 90%.

(3-Ethoxycarbonylbenzyl)zinc Chloride (**136c**)



According to TP2 ethyl 3-(chloromethyl)benzoate (**136c**) (0.396 g, 2.00 mmol) in THF (2.5 mL) was added to a mixture of activated zinc powder (0.261 g, 4.00 mmol), LiCl (0.106 g, 3.00 mmol) and THF (2.5 mL). After 12 h at 25 °C the reaction was finished and iodometric titration indicates a concentration of 0.32 M, which corresponds to a yield of 80%.

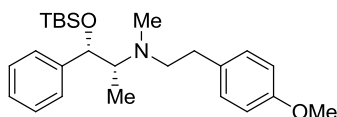
((6-Chloropyridin-3-yl)methyl)zinc Chloride (**136e**)



2-chloro-5-(chloromethyl)pyridine hydrochloride (0.492 g, 2.50 mmol) (**136e**) - was solved in water and the solution was basified with sat. aq. NaHCO₃ solution. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), the combined organic layers were dried with MgSO₄ and the solvent was removed *in vacuo*. The dried product was added to a mixture of activated zinc powder (0.261 g, 4.00 mmol), LiCl (0.106 g, 3.00 mmol) and THF (2.5 mL) as a solution in THF (2.5 mL) at 0 °C. The reaction mixture was warmed to 25 °C and after 12 h the reaction was finished. Iodometric titration indicates a concentration of 0.33 M, which corresponds to a yield of 66%.

7.4 Preparation of Tertiary Ephedrine Derivatives of Type 145

(1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(4-methoxyphenethyl)-*N*-methyl-1-phenylpropan-2-amine (**145a**)



Prepared according to **TP4** from (+)-**141** (306 mg, 1.10 mmol, 1.1 equiv) and (4-methoxybenzyl)zinc chloride (**136b**, 1.96 mL, 0.560 M in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO₂, *n*hexane/EtOAc = 20:1) afforded **145a** as a colorless oil (350 mg, 85%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.26–7.17 (m, 5H), 6.94 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.57 (d, J = 5.9 Hz, 1H), 3.72 (s, 3H), 2.79–2.70 (m, 1H), 2.59–2.36 (m, 4H), 2.23 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.36 (s, 3H).

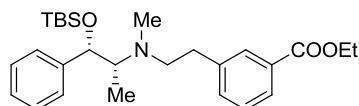
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 157.9, 145.1, 133.1, 130.0, 129.7, 127.7, 126.9, 113.8, 77.4, 65.4, 56.9, 55.4, 38.1, 34.2, 26.0, 18.3, 9.2, -4.2, -4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2953 (m), 2929 (m), 2865 (m), 1690 (w), 1612 (w), 1511 (s), 1462 (m), 1360 (w), 1300 (w), 1245 (vs), 1176 (m), 1110 (w), 1081 (s), 1060 (vs), 1039 (s), 1005 (m), 863 (s), 832 (vs), 774 (vs), 737 (m), 698 (s), 668 (m).

MS (EI, 70 eV): m/z (%) = 398.3 (1), 292.1 (5), 192.2 (100), 135.1 (30), 105.1 (6), 73.2 (10).

HRMS (EI): m/z calc. for [C₂₅H₃₈NO₂Si]⁺: 412.2666; found 412.2674.

Ethyl 3-(((1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)ethyl)benzoate (145b**)**



Prepared according to **TP4** from (+)-**141** (158 mg, 0.550 mmol, 1.1 equiv) and (3-Ethoxycarbonylbenzyl)zinc chloride (**136c**, 1.56 mL, 0.300 M in THF, 0.550 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO₂, *n*hexane/EtOAc = 20:1) afforded **145b** as a colorless oil (196 mg, 81%).

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.84 (d, J = 7.7), 7.80 (s, 1H), 7.30–7.16 (m, 7H), 4.60 (d, J = 6.0, 1H), 4.38 (q, J = 7.1, 2H), 2.83–2.77 (m, 1H), 2.66–2.51 (m, 4H), 2.30 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 6.7, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.31 (s, 3H).

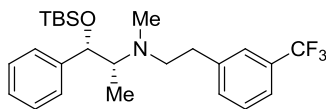
¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 167.0, 145.0, 141.3, 133.4, 130.5, 129.9, 128.3, 127.7, 127.2, 126.9, 77.2, 65.4, 61.0, 56.4, 38.0, 34.9, 26.0, 18.3, 14.5, 9.4, -4.2, -4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2955 (m), 2929 (m), 2856 (m), 1718 (vs), 1605 (w), 1587 (w), 1462 (m), 1366 (m), 1274 (vs), 1257 (s), 1194 (s), 1104 (s), 1082 (s), 1060 (vs), 1026 (s), 1005 (m), 863 (s), 834 (vs), 774 (vs), 749 (m), 697 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 440.3 (1), 410.3 (1), 234.2 (100), 177.1 (4), 149.1 (6), 131.1 (6), 105.1 (5), 73.1 (7).

HRMS (EI): m/z calc. for [C₂₆H₃₈NO₃Si]⁺: 440.2621; found 440.2616.

((1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-methyl-1-phenyl-*N*-(3-(trifluoromethyl)phenethyl)propan-2-amine (145c)



Prepared according to **TP4** from (+)-**141** (158 mg, 0.550 mmol, 1.1 equiv) and (3-(trifluoromethyl)benzyl)zinc chloride (**136d**, 0.350 mL, 1.43 M in THF, 0.550 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 30:1) afforded **145c** as a colorless oil (187 mg, 83%).

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.41 (d, J = 7.9, 1H), 7.35 (s, 1H), 7.34–7.18 (m, 7H), 4.59 (d, J = 6.0 Hz, 1H), 2.80 (p, J = 6.5 Hz, 1H), 2.68–2.50 (m, 4H), 2.29 (s, 3H), 1.06 (d, J = 6.5 Hz, 3H), 0.86 (s, 8H), 0.02 (s, 3H), –0.31 (s, 3H).

¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 144.8, 141.8, 132.1, 130.3 (q, J = 31.8 Hz), 128.5, 127.6, 126.7, 125.3, 124.2 (q, J = 273.3 Hz) 122.6, 77.1, 65.3, 56.2, 37.8, 34.7, 25.8, 18.1, 9.2, –4.4, –5.0.

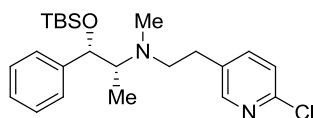
¹⁹F-NMR (376 MHz, CDCl₃): δ / ppm = –62.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{–1} = 2955 (m), 2930 (m), 2857 (m), 1493 (w), 1471 (w), 1450 (m), 1326 (s), 1320 (s), 1256 (m), 1198 (m), 1163 (s), 1123 (vs), 1071 (s), 1061 (s), 1027 (w), 1005 (w), 908 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 436.4 (1), 320.3 (2), 230.2 (100), 173.1 (7), 153.1 (6), 133.1 (5), 73.1 (5).

HRMS (EI): m/z calc. for [C₂₄H₃₃F₃N₂OSi]⁺: 436.2284; found 436.2282.

(1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(2-(6-chloropyridin-3-yl)ethyl)-*N*-methyl-1-phenylpropan-2-amine (145d)



Prepared according to **TP4** from (+)-**141** (306 mg, 1.10 mmol, 1.1 equiv) and (3-((6-chloropyridin-3-yl)methyl)zinc chloride (3.33 mL, 0.330 M in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 20:1) afforded the title compound as a colorless oil (313 mg, 75%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 8.03 (dd, J = 2.5, 0.7 Hz, 1H), 7.29–7.16 (m, 5H), 7.11 (dd, J = 8.2, 2.5 Hz, 1H), 7.04 (dd, J = 8.2, 0.7 Hz), 4.50 (d, J = 6.9 Hz), 2.77 (p, J = 6.7 Hz, 1H), 2.67–2.39 (m, 4H), 2.23 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), –0.33 (s, 3H).

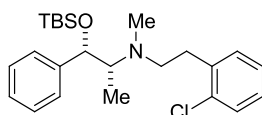
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 149.7, 148.8, 144.8, 139.2, 135.3, 127.8, 127.0, 126.9, 123.7, 77.4, 65.5, 56.1, 37.1, 30.9, 26.0, 18.2, 9.5, –4.3, –4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954 (m), 2928 (m), 2855 (m), 1585 (w), 1564 (w), 1458 (s), 1381 (m), 1360 (w), 1250 (s), 1209 (w), 1103 (s), 1082 (s), 1059 (vs), 1025 (s), 1005 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 403.2 (1), 287.1 (2), 197.1 (100), 140.1 (12), 104.1 (4), 73.1 (7), 56.1 (2).

HRMS (EI): m/z calc. for $[\text{C}_{23}\text{H}_{34}\text{ClN}_2\text{OSi}]^+$: 417.2123; found 417.2129.

(1S, 2R)-1-((*tert*-Butyldimethylsilyl)oxy)-N-(2-chlorophenethyl)-N-methyl-1-phenylpropan-2-amine (145e)



Prepared according to **TP4** from (+)-**141** (279 mg, 1.0 mmol, 1.0 equiv) and 2-chlorobenzylzinc chloride (**136f**, 0.69 mL, 1.60 M in THF, 1.1 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3 , *isohexane*/EtOAc = 49:1) afforded **145e** as a colorless oil (380 mg, 91%).

^1H -NMR (300 MHz, CDCl_3) δ /ppm = 7.34-7.23 (m, 6H), 7.15-7.08 (m, 3H), 4.63 (d, J = 5.9 Hz, 1H), 2.81 (qi, J = 6.6 Hz, 1H), 2.71-2.61 (m, 4H), 2.32 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 3H), -0.30 (s, 3H).

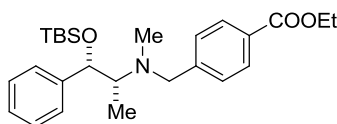
^{13}C -NMR (75 MHz, CDCl_3) δ /ppm = 145.3, 138.7, 134.2, 131.2, 129.6, 127.9, 127.6, 127.1, 127.0, 127.0, 65.8, 54.6, 38.4, 33.0, 26.2, 18.4, 9.7, -4.0, -4.6.

IR (cm^{-1}): $\tilde{\nu}$ = 2956, 2929, 2886, 2856, 2796, 1472, 1360, 1251, 1082, 1053, 1028, 1006, 863, 834, 816, 774, 747, 698, 680, 675.

MS (70 eV, EI) m/z (%) = 417 (1) [M^+], 402 (1), 198 (35), 197 (12), 196 (100), 139 (19), 103 (12), 73 (17).

HRMS for $\text{C}_{24}\text{H}_{36}^{35}\text{ClNOSi}$ (402.2025, [$\text{M}-\text{CH}_3$] $^+$): found: 402.2024.

Ethyl 4-(((1S, 2R)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)methyl)benzoate (145f)



Prepared according to **TP4** from (+)-**141** (279 mg, 1.0 mmol, 1.0 equiv) and (4-(ethoxycarbonyl)phenyl)zinc chloride (1.7 mL, 0.65 M in THF, 1.1 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3 , *isohexane*/EtOAc = 99:1) afforded the title compound as a colorless oil (309 mg, 70%).

¹H-NMR (300 MHz, CDCl₃) δ /ppm = 7.80 (d, J = 8.4 Hz, 2H), 7.28-7.20 (m, 5H), 6.96 (d, J = 8.4 Hz, 2H), 4.56 (d, J = 7.2 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 3.60-3.46 (m, 2H), 2.79 (qi, J = 6.6 Hz, 1H), 2.12 (s, 3H), 1.35 (t, J = 7.0, 3H), 1.11 (d, J = 6.6 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H).

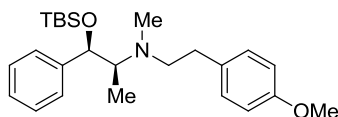
¹³C-NMR (75 MHz, CDCl₃) δ /ppm = 166.7, 145.8, 144.8, 129.2, 128.7, 128.1, 127.6, 126.9, 126.9, 64.9, 60.7, 58.7, 37.3, 25.8, 18.1, 14.4, 9.1, -4.4, -5.0.

IR (cm⁻¹): $\tilde{\nu}$ = 2957, 2930, 2857, 2794, 1717, 1611, 1472, 1452, 1413, 1365, 1272, 1258, 1172, 1105, 1098, 1084, 1060, 1020, 863, 834, 775, 756, 699.

MS (70 eV, EI) m/z (%) = 441 (1) [M⁺], 221 (15), 220 (100), 163 (28), 73 (7).

HRMS for C₂₆H₃₉NO₃Si (440.2626, [M-H]⁺): found: 440.2616.

(1R, 2S)-1-((*tert*-Butyldimethylsilyl)oxy)-N-(4-methoxyphenethyl)-N-methyl-1-phenylpropan-2-amine (145g)



Prepared according to **TP4** from (+)-**141** (306 mg, 1.10 mmol, 1.1 equiv) and (4-methoxybenzyl)zinc chloride (**136b**, 1.96 mL, 0.560 M in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 20:1) afforded **145g** as a colorless oil (350 mg, 85%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.26–7.17 (m, 5H), 6.94 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.57 (d, J = 5.9 Hz, 1H), 3.72 (s, 3H), 2.79–2.70 (m, 1H), 2.59–2.36 (m, 4H), 2.23 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.36 (s, 3H).

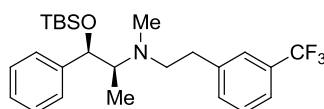
¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 157.9, 145.1, 133.1, 129.7, 127.7, 126.9, 126.4, 113.8, 77.4, 65.4, 56.9, 55.4, 38.1, 34.2, 26.0, 18.3, 9.2, -4.2, -4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2953 (m), 2929 (m), 2865 (m), 1690 (w), 1612 (w), 1511 (s), 1462 (m), 1360 (w), 1300 (w), 1245 (vs), 1176 (m), 1110 (w), 1081 (s), 1060 (vs), 1039 (s), 1005 (m), 863 (s), 832 (vs), 774 (vs), 737 (m), 698 (s), 668 (m).

MS (EI, 70 eV): m/z (%) = 398.3 (1), 292.1 (5), 192.2 (100), 135.1 (30), 105.1 (6), 73.2 (10).

HRMS (EI): m/z calc. for [C₂₅H₃₈NO₂Si]⁺: 412.2666; found 412.2674.

((1R, 2S)-1-((*tert*-Butyldimethylsilyl)oxy)-N-methyl-1-phenyl-N-(3-(trifluoromethyl)phenethyl)propan-2-amine (145h)



Prepared according to **TP4** from (+)-**141** (158 mg, 0.550 mmol, 1.1 equiv) and (3-(trifluoromethyl)benzyl)zinc chloride (**136d**, 0.350 mL, 1.43 M in THF, 0.550 mmol, 1.1 equiv).

Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 30:1) afforded **145h** as a colorless oil (187 mg, 83%).

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.41 (d, J = 7.9, 1H), 7.35 (s, 1H), 7.34–7.18 (m, 7H), 4.59 (d, J = 6.0 Hz, 1H), 2.80 (p, J = 6.5 Hz, 1H), 2.68–2.50 (m, 4H), 2.29 (s, 3H), 1.06 (d, J = 6.5 Hz, 3H), 0.86 (s, 8H), 0.02 (s, 3H), -0.31 (s, 3H).

¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 144.8, 141.8, 132.1, 130.3 (q, J = 31.8 Hz), 128.5, 127.6, 126.7, 125.3, 124.2 (q, J = 273.3 Hz), 122.6, 77.1, 65.3, 56.2, 37.8, 34.7, 25.8, 18.1, 9.2, -4.4, -5.0.

¹⁹F-NMR (376 MHz, CDCl₃): δ / ppm = -62.48.

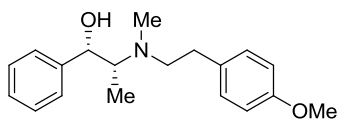
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2955 (m), 2930 (m), 2857 (m), 1493 (w), 1471 (w), 1450 (m), 1326 (s), 1320 (s), 1256 (m), 1198 (m), 1163 (s), 1123 (vs), 1071 (s), 1061 (s), 1027 (w), 1005 (w), 908 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): m/z (%) = 436.4 (1), 320.3 (2), 230.2 (100), 173.1 (7), 153.1 (6), 133.1 (5), 73.1 (5).

HRMS (EI): m/z calc. for [C₂₄H₃₃F₃N₂OSi]⁺: 436.2284; found 436.2282.

7.5 Deprotection of the Alcohol Using TBAF

(1*S*, 2*R*)-2-((4-Methoxyphenethyl)(methyl)amino)-1-phenylpropan-1-ol (**146a**)



Prepared according to **TP5** from **145a** (290 mg, 0.700 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 5:1) afforded **146a** as a white solid (208 mg, 99%).

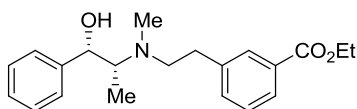
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.35–7.21 (m, 5H), 7.08 (d, J = 8.6 Hz), 6.84 (d, J = 8.6 Hz, 2H), 4.76 (d, J = 4.3 Hz, 1H), 3.79 (s, 3H), 2.92–2.80 (m, 1H), 2.75–2.62 (m, 4H), 2.34 (s, 3H), 0.87 (d, J = 6.9 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 158.1, 142.3, 132.4, 129.7, 128.2, 126.9, 126.2, 114.0, 73.1, 63.7, 57.1, 55.4, 39.3, 33.3, 10.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2934 (m), 2834 (m), 2797 (m), 1611 (m), 1583 (w), 1511 (s), 1462 (m), 1451 (m), 1300 (m), 1244 (vs), 1176 (m), 1035 (w), 996 (w), 960 (w), 909 (m), 849 (w), 821 (s), 733 (s), 700 (s).

MS (EI, 70 eV): m/z (%) = 292.1 (4), 192.2 (100), 135.2 (40), 105.1 (4), 73.1 (8).

HRMS (EI): m/z calc. for [C₁₇H₂₀NO₂]⁺: 254.1545; found 254.1586.

Ethyl 3-(2-(((1*S*, 2*R*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)ethyl)benzoate (146b**)**

Prepared according to **TP5** from **145b** (156 mg, 0.340 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 5:1) afforded **146b** as a colorless oil (110 mg, 94%).

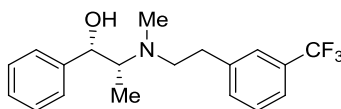
¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.90–7.79 (m, 2H), 7.37–7.14 (m, 7H), 4.74 (d, J = 4.3 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.57 (br, 1H), 2.91–2.82 (m, 1H), 2.82–2.65 (m, 4H), 2.34 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H).

¹³C-NMR (151 MHz, CDCl₃): δ / ppm = 166.7, 142.2, 140.5, 133.2, 130.6, 129.8, 128.4, 127.9, 127.4, 126.9, 126.1, 73.1, 63.6, 60.9, 56.5, 39.1, 33.8, 14.4, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2990 (w), 2937 (w), 2797 (w), 1714 (vs), 1604 (w), 1587 (w), 1449 (m), 1367 (m), 1273 (vs), 1195 (s), 1104 (s), 1083 (s), 1024 (m), 1000 (m), 909 (m), 864 (w), 817 (w), 749 (s), 731, (s), 698 (vs), 673 (m).

MS (EI, 70 eV): m/z (%) = 341.2 (1), 296.3 (6), 234.3 (100), 149.1 (10), 105.1 (10), 70.1 (8).

HRMS (EI): m/z calc. for [C₁₉H₂₂NO₂]⁺: 296.1651 ([M–OEt]⁺); found 296.1651.

(1*S*, 2*R*)-2-(Methyl(3-(trifluoromethyl)phenethyl)amino)-1-phenylpropan-1-ol (146c**)**

Prepared according to **TP5** from **145c** (157 mg, 0.350 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 5:1) afforded **146c** as a colorless oil (94 mg, 80%).

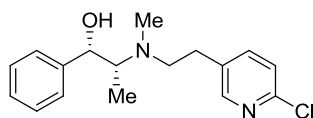
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.46–7.42 (m, 1H), 7.39–7.19 (m, 8H), 4.72 (d, J = 4.5 Hz, 1H), 3.22 (br, 1H), 2.85 (qd, J = 6.9, 4.5 Hz, 1H), 2.81–2.62 (m, 4H), 2.33 (s, 3H), 0.88 (d, J = 6.9 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 142.1, 141.1, 132.0, 130.7 (q, J = 32.0 Hz), 128.8, 127.8, 127.0, 126.1, 125.4 (q, J = 3.8 Hz), 124.2 (q, J = 271.5 Hz), 123.0 (q, J = 3.8 Hz), 73.3, 63.8, 56.3, 39.2, 34.0, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2963 (w), 2856 (w), 2800 (w), 1598 (w), 1493 (w), 1450 (m), 1377 (w), 1369 (w), 1329 (vs), 1199 (m), 1161 (s), 1119 (vs), 1072 (s), 1026 (m), 1000 (m), 907 (m), 883 (w), 798 (m), 761 (w), 734 (m), 699 (vs), 661 (m).

MS (EI, 70 eV): m/z (%) = 318.3 (1), 230.3 (100), 173.2 (12), 153.1 (8), 77.1 (3), 58.9 (4).

HRMS (EI): m/z calc. for [C₁₉H₂₂F₃NO]⁺: 336.1572; found 336.1569.

(1S, 2R)-2-((2-(6-Chloropyridin-3-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol (146d)

Prepared according to **TP5** from **145d** (253 mg, 0.600 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, *n*hexane/EtOAc = 5:1) afforded **146d** as a colorless oil (183 mg, 99%).

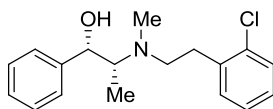
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 8.16 (dd, J = 2.5, 0.7 Hz, 1H), 7.36 (dd, J = 8.2, 2.5 Hz, 1H), 7.34–7.23 (m, 5H), 7.19 (dd, J = 8.2, 0.7 Hz, 1H), 4.73 (d, J = 4.8 Hz, 1H), 2.86 (qd, J = 6.8, 4.8 Hz), 2.73–2.60 (m, 4H), 2.34 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 149.7, 149.2, 142.2, 138.9, 134.5, 128.0, 127.1, 126.0, 123.8, 73.6, 63.8, 55.8, 38.8, 30.5, 9.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2963 (w), 2933 (w), 2897 (w), 1585 (m), 1565 (m), 1455 (vs), 1382 (m), 1360 (w), 1285 (w), 1210 (w), 1135 (m), 1103 (s), 1051 (m), 1024 (s), 996 (m), 915 (w), 824 (m), 798 (w), 761 (m), 736 (s), 700 (vs), 698 (w).

MS (EI, 70 eV): m/z (%) = 197.2 (100), 140.1 (26).

HRMS (EI): m/z calc. for [C₁₇H₁₉ClN₂]⁺: 286.1236; found 286.1227.

(1S,2R)-2-((2-Chlorophenethyl)(methyl)amino)-1-phenylpropan-1-ol (146e)

Prepared according to **TP5** from **145e** (100 mg, 0.239 mmol). Purification of the crude product by flash chromatography (SiO₂, *n*hexane/EtOAc = 20:1 + 2% NEt₃) afforded **146e** as a colorless oil (73 mg, 99%).

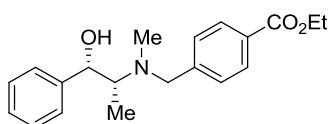
¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.36–7.29 (m, 4H), 7.26–7.14 (m, 4H), 4.98 (s, 1H), 3.09–2.76 (m, 5H), 1.33–1.19 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 141.9, 137.4, 134.1, 131.2, 129.7, 128.2, 128.1, 127.2, 127.1, 126.1, 72.8, 64.2, 54.8, 39.1, 31.3, 29.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3352 (w), 3062 (w), 3027 (w), 2933 (m), 2853 (w), 2799 (w), 1475 (m), 1450 (m), 1383 (w), 1248 (w), 1198 (w), 1156 (w), 1122 (m), 1052 (s), 1041 (m), 998 (m), 750 (vs), 701 (vs).

MS (EI, 70 eV): m/z (%) = 302 (M–H)⁺, 285 (31), 260 (30), 258 (100).

HRMS (EI): m/z calc. for [C₁₈H₂₁ClNO]⁺: 302.1317; found 302.1317 [(M–H)⁺].

Ethyl 4-(((1*S*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)methyl)benzoate (146f**)**

Prepared according to **TP5** from **145f** (100 mg, 0.239 mmol). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 20:1 + 2% NEt₃) afforded **146f** as a colorless oil (73 mg, 99%).

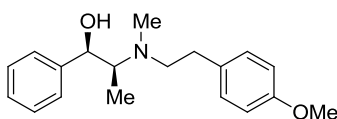
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.92–7.86 (m, 2H), 7.35–7.26 (m, 3H), 7.26–7.16 (m, 4H), 4.79 (d, J = 5.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.59 (s, 2H), 3.35–2.94 (m, 1H), 2.87 (qd, J = 6.8, 5.2 Hz, 1H), 2.14 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 166.7, 145.1, 142.8, 129.7, 129.3, 128.5, 128.2, 127.2, 126.3, 74.2, 63.8, 61.0, 58.8, 38.8, 14.5, 9.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2990, 2937, 2797, 1714, 1604, 1587, 1449, 1367, 1273, 1195, 1104, 1083, 1024, 1000, 909, 864, 817, 749, 731, 698, 673.

MS (EI, 70 eV): m/z (%) = 282 (4), 220 (100), 191 (3), 163 (59), 135 (11), 107 (12).

HRMS (EI): m/z calc. for [C₂₀H₂₄NO₃]⁺: 326.1762 ([M–H]⁺); found 326.1750.

(1*R*, 2*S*)-2-((4-Methoxyphenethyl)(methyl)amino)-1-phenylpropan-1-ol (146g**)**

Prepared according to **TP5** from **145g** (290 mg, 0.700 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, *i*hexane/EtOAc = 5:1) afforded **146g** as a white solid (208 mg, 99%).

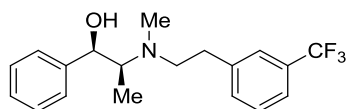
¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.35–7.21 (m, 5H), 7.08 (d, J = 8.6 Hz), 6.84 (d, J = 8.6 Hz, 2H), 4.76 (d, J = 4.3 Hz, 1H), 3.79 (s, 3H), 2.92–2.80 (m, 1H), 2.75–2.62 (m, 4H), 2.34 (s, 3H), 0.87 (d, J = 6.9 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 158.1, 142.3, 132.4, 129.7, 128.2, 126.9, 126.2, 114.0, 73.1, 63.7, 57.1, 55.4, 39.3, 33.3, 10.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2934 (m), 2834 (m), 2797 (m), 1611 (m), 1583 (w), 1511 (s), 1462 (m), 1451 (m), 1300 (m), 1244 (vs), 1176 (m), 1035 (w), 996 (w), 960 (w), 909 (m), 849 (w), 821 (s), 733 (s), 700 (s).

MS (EI, 70 eV): m/z (%) = 292.1 (4), 192.2 (100), 135.2 (40), 105.1 (4), 73.1 (8).

HRMS (EI): m/z calc. for [C₁₇H₂₀NO₂]⁺: 254.1545; found 254.1586.

(1*R*, 2*S*)-2-(Methyl(3-(trifluoromethyl)phenethyl)amino)-1-phenylpropan-1-ol (146h)

Prepared according to **TP5** from **145h** (157 mg, 0.350 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO₂, ihexane/EtOAc = 5:1) afforded **146h** as a colorless oil (94 mg, 80%).

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.46–7.42 (m, 1H), 7.39–7.19 (m, 8H), 4.72 (d, J = 4.5 Hz, 1H), 3.22 (br, 1H), 2.85 (qd, J = 6.9, 4.5 Hz, 1H), 2.81–2.62 (m, 4H), 2.33 (s, 3H), 0.88 (d, J = 6.9 Hz, 3H).

¹³C-NMR (101 MHz, CDCl₃): δ / ppm = 142.1, 141.1, 132.0, 130.7 (q, J = 32.0 Hz), 128.8, 127.8, 127.0, 126.1, 125.4 (q, J = 3.8 Hz), 124.2 (q, J = 271.5 Hz), 123.0 (q, J = 3.8 Hz), 73.3, 63.8, 56.3, 39.2, 34.0, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2963 (w), 2856 (w), 2800 (w), 1598 (w), 1493 (w), 1450 (m), 1377 (w), 1369 (w), 1329 (vs), 1199 (m), 1161 (s), 1119 (vs), 1072 (s), 1026 (m), 1000 (m), 907 (m), 883 (w), 798 (m), 761 (w), 734 (m), 699 (vs), 661 (m).

MS (EI, 70 eV): m/z (%) = 318.3 (1), 230.3 (100), 173.2 (12), 153.1 (8), 77.1 (3), 58.9 (4).

HRMS (EI): m/z calc. for [C₁₉H₂₂F₃NO]⁺: 336.1572; found 336.1569.

D. APPENDIX

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